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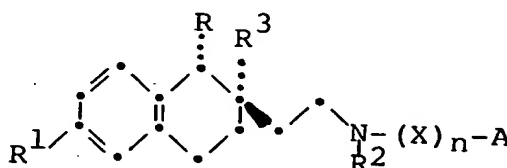
Print Name MATTHEW BOYER

Signature Matthew Boyer

TETRAHYDRONAPHTHALENE DERIVATIVES

BRIEF SUMMARY OF THE INVENTION

The invention relates to tetrahydronaphthalene derivatives of the formula



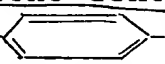
wherein R is lower-alkyl, R¹ is halogen, R² is C₁-C₁₂-alkyl, R³ is hydroxy, lower-alkoxy, lower-alkylcarbonyloxy, lower-alkoxy-lower-alkylcarbonyl oxy, lower-alkylaminocarbonyloxy, arylaminocarbonyloxy or aryl-lower-alkylaminocarbonyloxy, X is C₁-C₁₈-alkylene, C₁-C₁₈-alkylene which is interrupted by 1,4-phenylene or interrupted or lengthened by 1,4-cyclohexylene, A is di- or tri-substituted 2-imidazolyl attached via an ethylene group or a substituted or unsubstituted heterocycle selected from the group consisting of benzimidazolyl, benzimidazolonyl, imidazo[4,5-c]pyridinyl, imidazo[4,5-c]pyridinonyl, benzthiazolyl, benzodiazepine-2,5-dion-1-yl and pyrrolo[2,1-c][1,4]benzodiazepine-5,11-dion-10-yl and n is the number 0 or 1, in the form of racemates and optical antipodes, as well as N-oxides and pharmaceutically usable acid addition salts thereof.

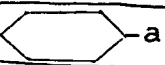
The compounds of formula I are useful as agents for the treatment or prevention of angina pectoris, ischaemia, arrhythmias, high blood pressure and cardiac insufficiency.

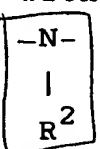
DETAILED DESCRIPTION OF THE INVENTION

As used herein, the term "lower-alkyl" - alone or in combination - denotes straight-chain and branched, saturated hydrocarbon groups with 1-6, preferably 1-4, carbon atoms such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec.-butyl, tert.-butyl and the like. The term " C_1-C_{12} -alkyl" denotes straight-chain and branched, saturated hydrocarbon groups with 1-12 carbon atoms. The term "lower-alkoxy" denotes lower-alkyl ether groups in which the term "lower-alkyl" is as described above. The term "halogen" denotes the four halogen atoms fluorine, chlorine, bromine and iodine. The term " C_1-C_{18} -alkylene" denotes straight-chain or branched, saturated hydrocarbon groups with 1-18 carbon atoms such as methylene, ethylene, propylene, methylethylene, butylene, 1,1-dimethylpropylene, pentamethylene, 1-methylpentamethylene, hexamethylene, heptamethylene, undecamethylene and the like. The term "aryl" denotes phenyl optionally mono- or multiply-substituted by halogen, trifluoromethyl, lower-alkyl, lower-alkoxy, nitro or amino. The term "aryl-lower-alkyl" denotes straight-chain or branched lower-alkyl groups in which one or more hydrogen atoms is/are replaced by aryl groups, such as benzyl, phenethyl and the like. Examples of optionally substituted benzimidazolyl, benzimidazolonyl, imidazo[4,5-c]pyridinyl, imidazo[4,5-c]pyridinonyl, benzthiazolyl, benzodiazepine-2,5-dion-1-yl or pyrrolo[2,1-c][1,4]benzodiazepine-5,11-dion-10-yl are 2-benzimidazolyl, 1-methyl-2-benzimidazolyl, 1-dodecyl-2-benzimidazolyl, benzimidazolonyl, 3-methylbenzimidazolonyl, 3-isopropylbenzimidazolonyl, 3-butylbenzimidazolonyl, 3-morpholinoethylbenzimidazolonyl, 3-benzylbenzimidazolonyl, 2-pyridylmethylbenzimidazolonyl, 2-imidazo[4,5-c]pyridinyl, imidazo[4,5-c]pyridinonyl, 2-benzthiazolyl, 2,3,4,5-tetrahydro-4-methylbenzodiazepine-2,5-dion-1-yl, 6-chloro-2,3,11,11a-tetrahydro-

-pyrrolo[2,1-c][1,4]benzodiazepine-5,11-dion-10-yl, 5,6-dimethyl-2-benzimidazolyl and the like. Examples of di- and tri-substituted 2-imidazolyl attached via an ethylene group are 1-methyl-4,5-diphenyl-2-imidazolyl-ethyl and 4,5-diphenyl-2-imidazolylethyl and the like. The term "leaving group" denotes conventional leaving groups such as halogen, preferably chlorine or bromine, arylsulphonyloxy such as, for example, tosyloxy, bromobenzenesulphonyloxy, benzenesulphonyloxy or mesitylenesulphonyloxy, or alkylsulphonyloxy such as, for example, mesyloxy or trifluoromethylsulphonyloxy. The term "N-oxide" denotes a compound wherein the nitrogen which is oxidized is the nitrogen which is attached via an ethylene to the tetrahydronaphthalene moiety. The terminology that X is C₁-C₁₈ alkylene which can be interrupted by 1,4-phenylene denotes that the moiety, X, can be

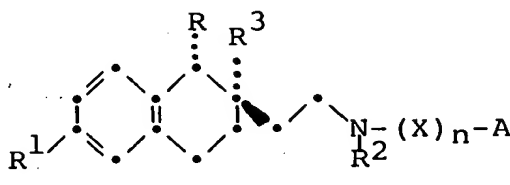
T0090X  -alkylene, wherein the total number of carbon atoms in the two alkylenes moieties together is not greater than 18. The terminology that X is C₁-C₁₈ alkylene which can be interrupted or lengthened by 1,4-cyclohexylene denotes that the moiety, X, can be

T0091X  -alkylene, or that X can be an alkylene moiety with cyclohexylene attached either to the A moiety or the

T0092X  moiety.

The term "pharmaceutically usable acid addition salt" denotes salts with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid, phosphoric acid, citric acid, formic acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulphonic acid, p-toluenesulphonic acid and the like. Such salts can be manufactured readily by any person skilled in the art having regard to the state of the art and taking into consideration the nature of the compound to be converted into a salt.

The invention relates to tetrahydronaphthalene derivatives of the formula



PSM
MIA
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LL

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wherein R is lower-alkyl, R¹ is halogen, R² is C₁-C₁₂-alkyl, R³ is hydroxy, lower-alkoxy, lower-alkylcarbonyloxy, lower-alkoxy-lower-alkylcarbonyl oxy, lower-alkylaminocarbonyloxy, arylaminocarbonyloxy or aryl-lower-alkylaminocarbonyloxy, X is C₁-C₁₈-alkylene, C₁-C₁₈-alkylene which is interrupted by 1,4-phenylene or interrupted or lengthened by 1,4-cyclohexylene, A is di- or tri-substituted 2-imidazolyl attached via an ethylene group or benzimidazolyl, substituted benzimidazolyl, benzimidazolonyl, imidazo[4,5-c]pyridinyl, imidazo[4,5-c]pyridinonyl, benzthiazolyl, benzodiazepine-2,5-dion-1-yl or pyrrolo[2,1-c][1,4]benzodiazepine-5,11-dion-10-yl and n is the number 0 or 1, in the form of racemates and optical antipodes, as well as N-oxides and pharmaceutically usable acid addition salts thereof.

The compounds of formula I are useful as calcium antagonists. More specifically, the compounds of formula I are useful as agents in the treatment or prevention of angina pectoris, ischaemia, arrhythmias, high blood pressure and cardiac insufficiency.

Those compounds of formula I in which R is isopropyl are preferred. R³ preferably is hydroxy, lower-alkyl-carbonyloxy, particularly isobutyryloxy, lower-alkoxy-lower-alkylcarbonyloxy, particularly methoxyacetyloxy, or lower-alkylaminocarbonyloxy, particularly butylamino-

carbonyloxy. n preferably is the number 1. Further, those compounds of formula I in which R¹ is fluorine are preferred. Those compounds of formula I in which R² is methyl are also preferred. The compounds of formula I in which X is C₃-C₇-alkylene, particularly propylene, butylene, pentamethylene or hexamethylene, are likewise preferred. A preferably signifies 2-benzimidazolyl, 2-benzthiazolyl, 1-methyl-2-benzimidazolyl, 1-dodecyl-2-benzimidazolyl, benzimidazolonyl, 2,3,4,5-tetrahydro-4-methylbenzodiazepine-2,5-dion-1-yl, 6-chloro-2,3,11,11a-tetrahydro-pyrrolo[2,1-c][1,4]benzodiazepine-5,11-dion-10-yl or 1-methyl-4,5-diphenyl-2-imidazolyl, particularly 2-benzimidazolyl or 2-benzthiazolyl.

More, preferred are those compounds of formula I in which R is isopropyl, R³ is hydroxy, isobutyryloxy, methoxyacetyloxy or butylaminocarbonyloxy, R¹ is fluorine, R² is methyl, X is propylene, butylene, pentamethylene or hexamethylene, A is 2-benzimidazolyl or 2-benzthiazolyl and n is the number 1.

Especially preferred compounds of formula I are:

2-[2-[[3-(2-Benzimidazolyl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1 α -isopropyl-2 α -naphthyl methoxyacetate;

[1S,2S]-2-[2-[[5-(2-benzthiazolyl)pentyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate; and

[1S,2S]-2-[2-[[3-(2-benzimidazolyl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate.

Exemplary of other compounds of formula I are:

[1S,2S]-2-[2-[[7-(2-benzimidazolyl)heptyl]methylamino]-ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-1-naphthalenol;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[5-(1-methyl-2-benzimidazolyl)pentyl]amino]-ethyl]-2-naphthyl butylcarbamate;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[6-(2-oxo-1-benzimidazoliny)hexyl]amino]-ethyl]-2-naphthyl methoxyacetate;

[1S,2S]-2-[2-[[3-(2-benzimidazolyl)propyl]methyl-N-oxidoamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate;

[1S,2S]-2-[2-[[7-(1-dodecyl-2-benzimidazolyl)heptyl]-methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[[3-(1-methyl-4,5-diphenylimidazol-2-yl)propyl]methylamino]ethyl]-2-naphthyl methoxyacetate;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[[4-[(2-benzimidazolyl)methyl]benzyl]methylamino]ethyl]-2-naphthyl methoxyacetate;

[1S,2S]-2-[2-[[3-(2-benzimidazolyl)propyl]methylamino]-ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol;

[1S,2S]-2-[2-[[3-(2-benzimidazolyl)propyl]methylamino]-ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate;

[1S,2S]-2-[2-[[5-(2-benzimidazolyl)pentyl]methylamino]-ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol;

[1S,2S]-2-[2-[[5-(2-benzimidazolyl)pentyl]methylamino]-ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate;

[1S,2S]-2-[2-[[4-(2-benzimidazolyl)butyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol;

[1S,2S]-2-[2-[[11-(2-benzimidazolyl)undecyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol;

[1S,2S]-2-[2-[[7-(5,6-dimethyl-2-benzimidazolyl)-heptyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol;

[1S,2S]-2-[2-[[5-(2-benzimidazolyl)pentyl]dodecylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[[7-(1H-imidazo[4,5-c]pyridin-2-yl)heptyl]methylamino]ethyl]-2-naphthalenol;

[1S,2S]-2-[2-[[4-(2-Benzimidazolyl)butyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate;

[1S,2S]-2-[2-[[7-(2-benzimidazolyl)heptyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate;

[1S,2S]-2-[2-[[11-(2-benzimidazolyl)undecyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate;

[1S,2S]-2-[2-[[7-(5,6-dimethyl-2-benzimidazolyl)-heptyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate;

[1S,2S]-2-[2-[[5-(2-benzimidazolyl)pentyl]dodecylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[[7-(1H-imidazo[4,5-c]pyridin-2-yl)heptyl]methylamino]ethyl]-2-naphthyl methoxyacetate;

[1S,2S]-2-[2-[[3-(2-benzthiazolyl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol;

[1S,2S]-2-[2-[[5-(2-benzthiazolyl)pentyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol;

[1S,2S]-2-[2-[[7-(2-benzthiazolyl)heptyl]methylamino]-ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol;

[1S,2S]-2-[2-[[3-(2-benzthiazolyl)propyl]methylamino]-ethyl]-6-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate;

[1S,2S]-2-[2-[[7-(2-benzthiazolyl)heptyl]methylamino]-ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate;

[1S,2S]-2-[2-[[[(S)-5-(2-benzimidazolyl)-1-methylpentyl]-methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol;

[1S,2S]-2-[2-[[[(S)-5-(2-benzimidazolyl)-1-methylpentyl]-methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate;

[1S,2S]-2-[2-[[7-(2-benzimidazolyl)heptyl]methylamino]-ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-methoxynaphthalenol;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[5-(1-methyl-2-benzimidazolyl)pentyl]amino]ethyl]-2-naphthalenol;

[1S,2S]-2-[2-[[7-(1-dodecyl-2-benzimidazolyl)heptyl]-methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-methyl-[5-(1-methyl-2-benzimidazolyl)pentyl]amino]ethyl]-2-naphthyl methoxyacetate;

[1S,2S]-2-[2-[(2-benzthiazolyl)methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol;

1-[2-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]methylamino]ethyl]-2-benzimidazolinone;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[2-(2-oxo-1-benzimidazoliny)]ethyl]amino]ethyl]-2-naphthyl methoxyacetate;

1-[6-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]methylamino]hexyl]-2-benzimidazolinone;

1-[6-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]methylamino]hexyl]-3-methyl-2-benzimidazolinone;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[[4-[p-(imidazol-1-yl)phenyl]butyl]methylamino]ethyl]-2-naphthalenol;

1-[4-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]methylamino]butyl]-2-benzimidazoline;

1-[4-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]methylamino]butyl]-3-isopropyl-2-benzimidazolinone;

1-[6-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]methylamino]hexyl]-3-butyl-2-benzimidazolinone;

1-[6-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]methylamino]hexyl]-3-(2-morpholinoethyl)-2-benzimidazolinone;

1-benzyl-3-[4-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]methylamino]butyl]-2-benzimidazolinone;

1-[4-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]methylamino]butyl]-3-(2-pyridylmethyl)-2-benzimidazolinone;

3-[6-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]methylamino]hexyl]-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[4-(2-oxo-1-benzimidazoliny)]butyl]amino]ethyl]-2-naphthyl methoxyacetate;

[1S,2S]-2-[2-[6-(1,2-dihydro-2-oxo-3H-imidazo[4,5-c]pyridin-3-yl)hexyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[6-(3-methyl-2-oxo-1-benzimidazoliny)]hexyl]amino]-ethyl]-2-naphthyl methoxyacetate;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-
5 -[[4-[p-(imidazol-1-yl)phenyl]butyl]methylamino]ethyl]-2-naphthyl methoxyacetate;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[4-(3-isopropyl-2-oxo-1-benzimidazoliny)]-butyl]amino]ethyl]-2-naphthyl methoxyacetate;

10 [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[6-(3-butyl-2-oxo-1-benzimidazoliny)]hexyl]-amino]ethyl]-2-naphthyl methoxyacetate;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[6-[3-(2-morpholinoethyl)-2-oxo-1-benzimidazoliny]]hexyl]amino]ethyl]-2-naphthyl methoxyacetate;

15 [1S,2S]-2-[2-[[4-(3-benzyl-2-oxo-1-benzimidazoliny)]-butyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[4-[2-oxo-3-(2-pyridylmethyl)-1-benzimidazoliny]]-butyl]amino]ethyl]-2-naphthyl methoxyacetate;

[1S,2S]-2-[2-[[3-(2-benzimidazolyl)propyl]methylamino]-ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl isobutyrate;

25 [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[5-(1-methyl-2-benzimidazolyl)pentyl]amino]-ethyl]-2-naphthyl carbanilate;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[5-(1-methyl-2-benzimidazolyl)pentyl]amino]-ethyl]-2-naphthyl benzylcarbamate;

30 [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[5-(1-methyl-2-benzimidazolyl)pentyl]amino]-ethyl]-2-naphthyl p-chlorocarbanilate;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-
35 [[3-(4,5-diphenylimidazol-2-yl)propyl]methylamino]ethyl]-2-naphthyl methoxyacetate;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-
[[4-[(1-methyl-2-benzimidazolyl)methyl]benzyl]methyl-
amino]ethyl]-2-naphthyl methoxyacetate;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-
5 [2-[[4-[1-(1-methyl-2-benzimidazolyl)ethyl]benzyl]methyl-
amino]ethyl]-2-naphthyl methoxyacetate;

[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-
[methyl-[trans-4-(2-benzimidazolyl)cyclohexyl]methyl-
amino]ethyl]-2-naphthyl methoxyacetate;

10 [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-
[methyl-[trans-4-(1-methyl-2-benzimidazolyl)cyclohexyl]-
methylamino]ethyl]-2-naphthyl methoxyacetate;

1-[4-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-
1-isopropyl-2-naphthyl]ethyl]methylamino]butyl]-3,4-
15 dihydro-4-methyl-2H-1,4-benzodiazepine-2,5(1H)-dione;

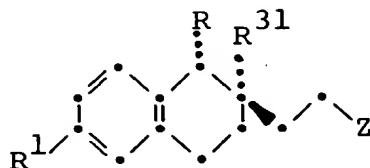
(S)-6-chloro-10-[4-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetra-
hydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]methylamino]-
butyl]-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzo-
diazepine-5,11-(10H)-dione;

20 [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-
[[4-(2,3,4,5-tetrahydro-4-methyl-2,5-dioxo-1H-1,4-benzodia-
zepin-1-yl)butyl]methylamino]ethyl]-2-naphthyl methoxy-
acetate; and

[1S,2S]-2-[2-[[4-[(S)-6-chloro-2,3,11,11a-tetrahydro-
25 5,11-dioxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-10(5H)-
yl]butyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-
isopropyl-2-naphthyl methoxyacetate.

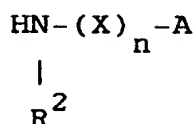
The compounds of formula I in the form of racemates
30 and optical antipodes, as well as N-oxides and pharma-
ceutically usable acid addition salts thereof can be
prepared as follows:

a) for the making of compounds of formula I in which R^3 is hydroxy or lower-alkoxy and R , R^1 , R^2 , A , X and n are as described above, reacting a compound of the formula



II

wherein R^{31} is hydroxy or lower-alkoxy and Z is a leaving group and R and R^1 are as described above, with an amine of the formula

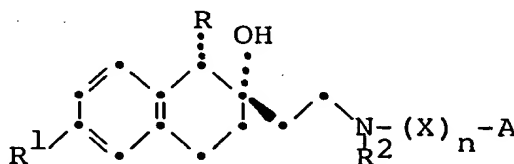


III

wherein R^2 , A , X and n are as described above,

or

b) for the making of compounds of formula I in which R^3 is lower-alkylcarbonyloxy or lower-alkoxy-lower-alkylcarbonyloxy and R , R^1 , R^2 , A , X and n are as described above reacting a compound of the formula



Ia

wherein R , R^1 , R^2 , A , X and n are as described above,

with an acylating agent yielding a lower-alkylcarbonyl or lower-alkoxy-lower-alkylcarbonyl group, or

c) for the making of compounds of formula I in which R^3 is lower-alkylaminocarbonyloxy, arylaminocarbonyloxy or

H aryl-lower-alkylaminocarbonyloxy and R, R¹, R², A, X and n are as described above, reacting a compound of formula Ia above with a lower-alkyl, aryl or aryl-lower-alkyl isocyanate, and, if desired,

5

PC d) oxidizing a compound obtained to the corresponding N-oxide, and/or

10

PC e) separating a racemate obtained into the optical antipodes, and/or

PC f) converting a compound obtained into a pharmaceutically usable acid addition salt.

15

P A compound of formula II is reacted with an amine of formula III according to conventional methods. The reaction is carried out in the presence or absence of an organic solvent which is inert under the reaction conditions at a temperature between about 20° and 150°C, preferably between about 80° and 120°C. Solvents such as dimethylformamide, dimethyl sulphoxide, alcohols such as isopropanol or tert.-butanol, ethers such as tetrahydrofuran or dioxan, aromatic hydrocarbons such as benzene, toluene or xylene, chlorinated hydrocarbons such as methylene chloride, carbon tetrachloride or chlorobenzene, and the like come into consideration in this reaction. The reaction is advantageously carried out in the presence of an acid-binding agent, for example a tertiary amine such as trimethylamine, triethylamine, ethyldiisopropylamine or 1,5-diazabicyclo[4.3.0]non-5-ene, whereby excess amine of formula III can also serve as the acid-binding agent. For reasons of convenience the reaction is carried out at atmospheric pressure, although higher pressure can also be used.

35

The acylation of a compound of formula Ia is also carried out according to conventional methods. Suitable

acylating agents are, in particular, activated acid derivatives such as acid halides and acid anhydrides or mixed acid anhydrides. The reaction is carried out in an organic solvent or solvent mixture which is inert under the reaction conditions at a temperature between about 0°C and the reflux temperature. As solvents there come into consideration, in particular, aromatic hydrocarbons such as benzene, toluene or xylene, chlorinated hydrocarbons such as methylene chloride or chloroform, ethers such as diethyl ether, tetrahydrofuran or dioxan, and the like.

The reaction of a compound of formula Ia with an isocyanate can also be effected according to conventional methods in an organic solvent or solvent mixture which is inert under the reaction conditions at a temperature between about 50°C and the boiling point of the solvent or solvent mixture, preferably between about 80 and 120°C, in the presence of a catalyst such as a tin-(II) salt, e.g. tin-(II) 2-ethylhexanoate. As solvents there come into consideration, in particular, aromatic hydrocarbons such as benzene, toluene or xylene, ethers such as tetrahydrofuran or dioxan, and the like.

A compound obtained can be converted into the corresponding N-oxide likewise in a conventional manner by means of an oxidation agent such as hydrogen peroxide or a peracid such as peracetic acid or perbenzoic acid in a solvent such as an alkanol, e.g. methanol or ethanol, and the like at a temperature between about 0° and 50°C, preferably at room temperature.

The starting materials of formulae II and III are known or can be obtained in accordance with known methods. A process for the preparation of a compound of formula III in which A is a heterocycle attached via a nitrogen atom or a carbon atom or di- or tri-substituted 2-imidazolyl attached via an ethylene group is outlined in Schemes

I-III hereinafter in which Boc denotes tert.butoxycarbonyl, Bz denotes benzyl and Ph denotes phenyl. With respect to the precise reaction conditions, reference is made to the experimental section.

5

The starting materials of formula IV, XI and XV in Schemes I-III are known.

10

15

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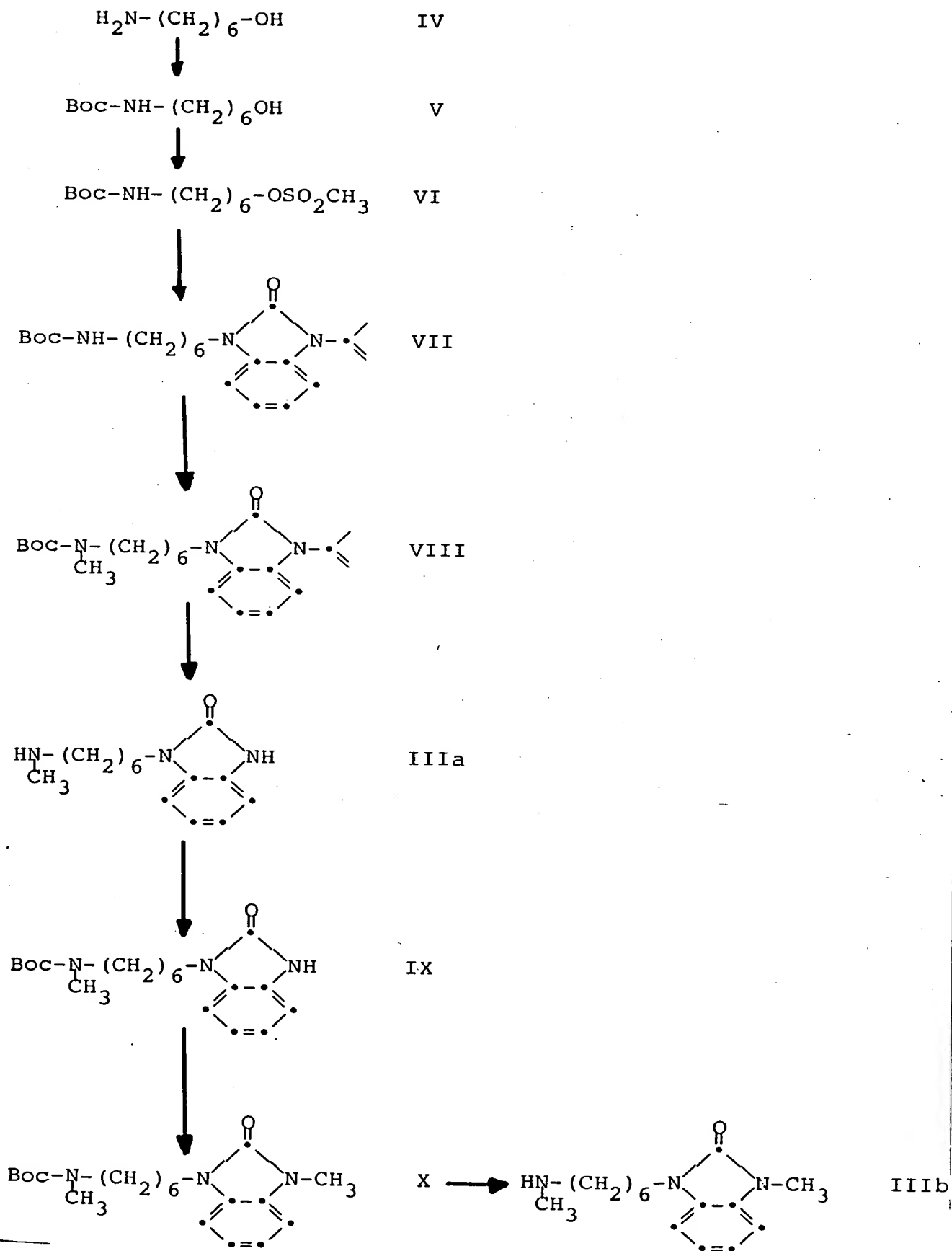
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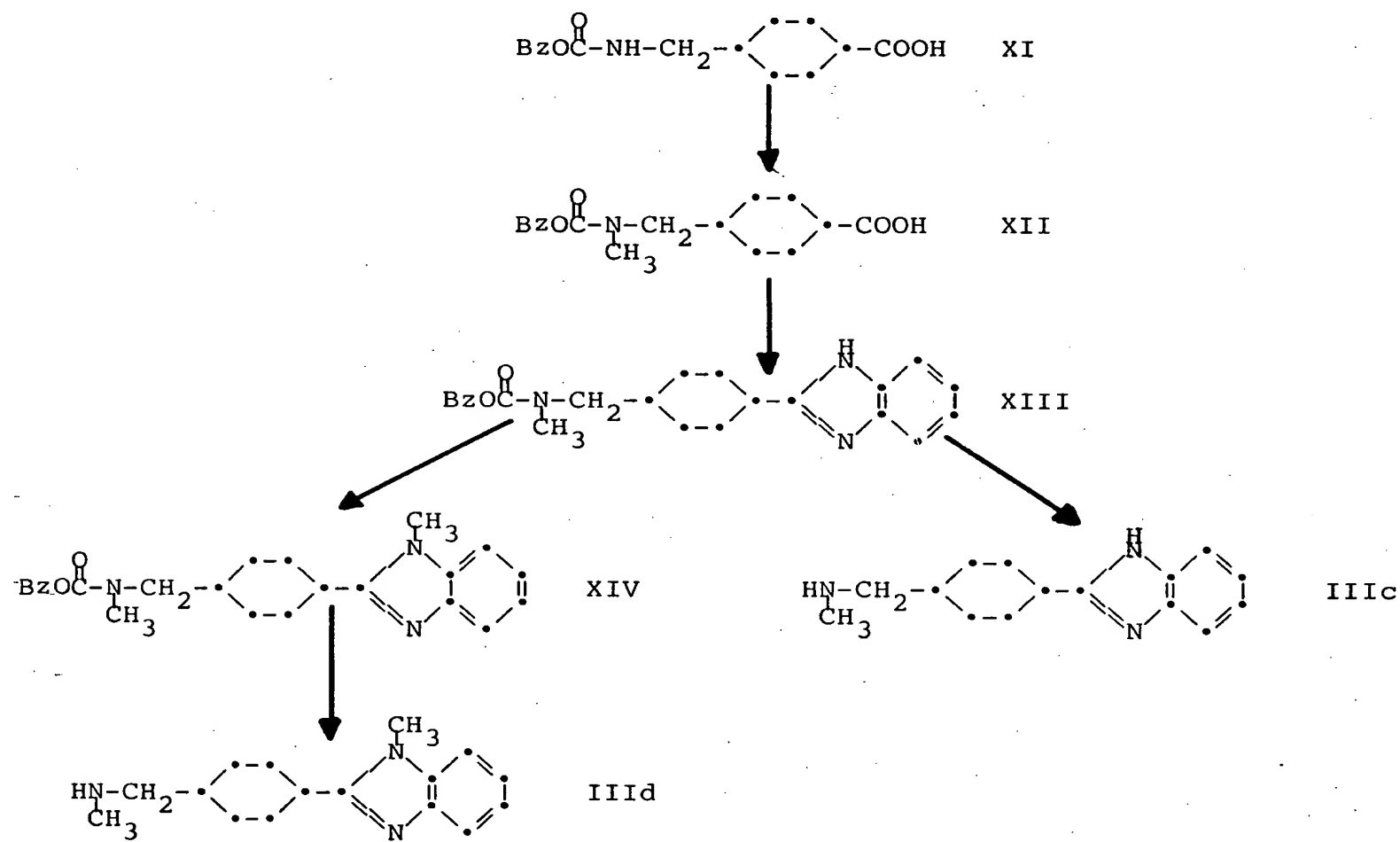
Scheme I



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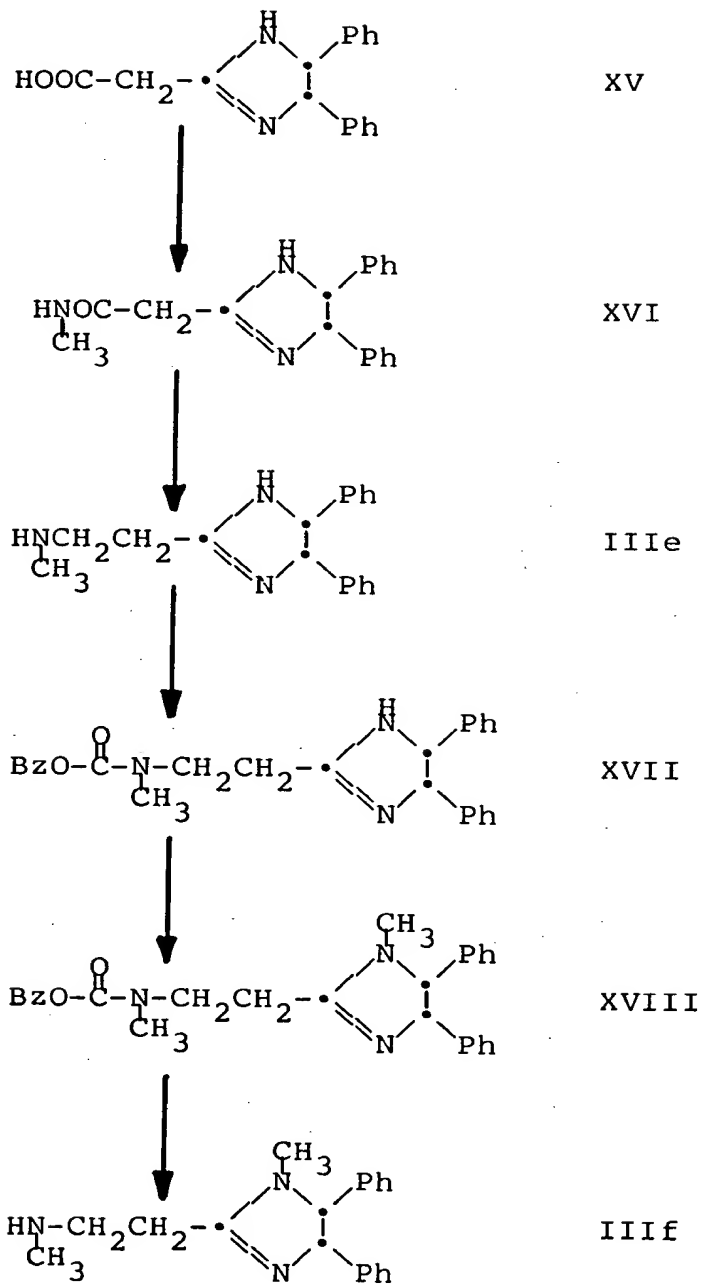
- 17 -

Scheme II



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Scheme III



9
The compounds of formula I contain at least one asymmetric centre (2-position) and can therefore exist as optical antipodes or as racemates. Compounds of formula I which contain more than one asymmetric centre are present
5 in the relative configuration indicated by formula I. The racemates of formula I can be resolved into the optical antipodes according to conventional methods, e.g. by reaction with an optically active acid and fractional crystallization of the salt obtained.

10

The compounds of formula I are characterized by valuable pharmacodynamic properties. In particular, the compounds of formula I have a pronounced calcium-antagonistic activity and can accordingly be used as
15 medicaments, especially for the control or prevention of angina pectoris, ischaemia, arrhythmias, high blood pressure and cardiac insufficiency.

The calcium-antagonistic activity as well as the blood
20 pressure-lowering properties of the compounds in accordance with the invention can be demonstrated in the tests described hereinafter:

25
A. ³H-Desmethoxyverapamil binding determinations:

25

30
The determination is carried out on partially-cleaned membranes of guinea pig heart. The reaction mixture (0.3 ml) consists of 0.2-0.8 mg of membrane protein, 2.5 nM of ³H-desmethoxyverapamil and various concentrations of test substances. The incubation lasts 120 minutes at 37°C and is stopped by dilution with the incubation buffer; a filtration is subsequently carried out. The filter-bound radioactivity is measured with a scintillation counter. Specific binding (i.e. receptor-
35 -bound) is defined as the difference between total and unspecific-bound radioactivity. The unspecific binding is determined in the presence of an excess of non-radioactive

82 verapamil (10 μ M).

M The activity (potency) of a compound in this test is defined by the IC_{50} value. The IC_{50} is the substance
5 concentration (in mol/l) which produces a half-maximum inhibition of the specific 3H -desmethoxyverapamil binding. This value is extrapolated from a concentration-binding curve.

10 B. Isolated, perfused guinea pig heart according to Langendorff:

P Guinea pigs weighing approximately 400 g are narcotized with Urethan (1 g/kg i.p.) and the heart is
15 removed rapidly. The aorta is cannulated and the heart is perfused retrogradely with a modified Krebs-Henseleit solution of the following composition in mM: NaCl 114.7, KCl 4.7, $MgSO_4$ 1.2, KH_2PO_4 1.5, $NaHCO_3$ 25, $CaCl_2$ 2.5 and glucose 11.1. The solution is gassed with
20 Oxycarbon (a mixture of 95% oxygen and 5% carbon dioxide) at pH 7.3 and a temperature of 37°C. The perfusion pressure is held constant at a value of 90 cm H_2O (8.83 kPa). A Miller microtip catheter pressure transducer (PC-350) is inserted in the left heart chamber in order to
25 measure the left ventricular pressure. The total coronary artery flow is collected in a funnel and measured with an electro magnetic flow meter. All measurement parameters are recorded on a recording apparatus (Gould, Model 2800). The test begins after an adaptation of 45 minutes.
30 Substances are infused with a velocity of 1% of the total coronary flow rate. A complete concentration-activity curve (10^{-10} to 10^{-6} M) is prepared for each substance. The two most important measurement parameters are:
M31 (1) CBF: coronary blood flow (in ml/min) - the velocity of
35 blood flow through the coronary arteries and (2) dp/dt: rate of increase in left ventricular pressure (in mmHg/sec), as a measurement of the contractility force of

21

the heart; this value is given as the % maximal variation from the initial value ($\Delta\%$) per dosage administered.

C. Haemodynamic parameters in the narcotized dog:

5 The 4 most important measurement parameters (with the respective measurement units) of the haemodynamic experiment are: (1) CBF: coronary blood flow (in ml/min) - the velocity of blood flow through the coronary arteries; 10 (2) HR: heart rate (in beats/min) - the heart frequency; (3) BP: blood pressure (in mm Hg) - the blood pressure; and (4) dp/dt: rate of increase in left ventricular pressure (in mm Hg/sec) as a measurement of the contracti- 15 lity force of the heart. The values are given as the % maximum variation from the initial value ($\Delta\%$) and the duration of this variation (t) per dosage administered.

There is thus obtained not only an overall picture of the activity of the substance, but also an estimation as 20 to the potential selectivity for a specific part of the circulatory system in the entire organism. After the administration of an anaesthetic, the dog is intubated and respired artificially. Blood pH, pCO_2 , pO_2 and haemoglobin are measured hourly with a blood-gas analyser. 25 The blood pressure (systolic and diastolic) is measured with a probe in the aorta abdominalis. The heart frequency is recorded by means of a tachometer, which is disengaged from the pressure pulse. For the other measurements the heart must be firstly be opened in order that a probe can 30 be inserted in the left ventricle (heart chamber) for the pressure measurements (dp/dt). The coronary blood flow is measured with a flowing probe in the left coronary artery (descendens).

35 The results obtained in these tests are compiled in the following Table:

Table

Compound	A	B		C				Dosage mg/kg i.v.
	IC ₅₀ [M]	CBF IC ₅₀ [M]	dp/dt Δ %	CBF Δ %	HR Δ %	BP Δ %	dp/dt Δ %	
A	$1.3 \cdot 10^{-7}$	$4.7 \cdot 10^{-8}$	250	86	- 7	-22	25	0.3
B	$6.3 \cdot 10^{-7}$	$5.0 \cdot 10^{-8}$	216	36	0	- 6	8	0.3
C	$2.1 \cdot 10^{-7}$	$1.7 \cdot 10^{-8}$	192	62	- 9	-16	15	0.3
D	$3.2 \cdot 10^{-8}$	$1.1 \cdot 10^{-9}$	162	22	-25	-21	6	0.03
E	$1.0 \cdot 10^{-6}$	$1.0 \cdot 10^{-5}$	164	57	0	- 8	10	1
F	$3.4 \cdot 10^{-8}$	$2.8 \cdot 10^{-8}$	130	46	- 2	- 3	4	0.3
G	$1.5 \cdot 10^{-7}$	$1.8 \cdot 10^{-9}$	237	96	-15	-20	11	0.3
H	$2.8 \cdot 10^{-8}$	$2.4 \cdot 10^{-9}$	222	146	-41	-28	25	0.3
I	$1.0 \cdot 10^{-7}$	$2.2 \cdot 10^{-8}$	124	82	- 9	-14	18	0.3

A = [1S,2S]-2-[2-[[3-(2-Benzimidazolyl)propyl]methylamino]-ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate

B = [1S,2S]-2-[2-[[7-(2-Benzimidazolyl)heptyl]methylamino]-ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol

C = [1S,2S]-6-Fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[5-(1-methyl-2-benzimidazolyl)pentyl]amino]-ethyl]-2-naphthyl butylcarbamate

D = [1S,2S]-6-Fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[6-(2-oxo-1-benzimidazoliny)hexyl]amino]-ethyl]-2-naphthyl methoxyacetate

- E = [1S,2S]-2-[2-[[3-(2-Benzimidazolyl)propyl]methyl-N-
-oxidoamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-iso-
propyl-2-naphthyl methoxyacetate
- F = [1S,2S]-2-[2-[[7-(1-Dodecyl-2-benzimidazolyl)heptyl]-
5 methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-iso-
propyl-2-naphthyl methoxyacetate
- ~~G = [1S,2S]-6-Fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-
-[[3-(1-methyl-4,5-diphenylimidazol-2-yl)propyl]methyl-
amino]ethyl]-2-naphthyl methoxyacetate~~
- 10 H = [1S,2S]-2-[2-[[5-(2-Benzthiazolyl)pentyl]methylamino]-
ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-
-naphthyl methoxyacetate
- I = [1S,2S]-6-Fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-
-[[4-[(2-benzimidazolyl)methyl]benzyl]methylamino]-
15 ethyl]-2-naphthyl methoxyacetate

BM
H3133
-
H3133
20 In the Table above, the IC_{50} of compound A in Test A
is given as $1.3 \cdot 10^{-7}$. This means 1.3×10^{-7} . All other
numbers which are similarly written have corresponding
meanings. Thus $4.7 \cdot 10^{-8}$ means 4.7×10^{-8} .

The compounds of formula I can be used as medicaments,
e.g. in the form of pharmaceutical preparations. The
pharmaceutical preparations can be administered orally,
25 e.g. in the form of tablets, coated tablets, dragees, hard
and soft gelatine capsules, solutions, emulsions or
suspensions. The administration can, however, also be
carried out rectally, e.g. in the form of suppositories,
or parenterally, e.g. in the form of injection solutions.

30

For the manufacture of tablets, coated tablets,
dragees and hard gelatine capsules the compounds of
formula I can be processed with pharmaceutically inert
excipients. A pharmaceutically inert excipient includes
35 inorganic or organic excipients or mixtures thereof. For
tablets, dragees and hard gelatine capsules, excipients
such as lactose, maize starch or derivatives thereof,

talc, stearic acid or its salts etc. may be used.

Suitable excipients for soft gelatine capsules are
e.g. vegetable oils, waxes, fats, semi-solid and liquid
5 polyols etc.

Suitable excipients for the manufacture of solutions
and syrups are e.g. water, polyols, saccharose, invert
10 sugar, glucose etc.

Suitable excipients for injection solutions are e.g.
water, alcohols, polyols, glycerine, vegetable oils etc.

Suitable excipients for suppositories are e.g. natural
15 or hardened oils, waxes, fats, semi-liquid or liquid
polyols etc..

Moreover, the pharmaceutical preparations can contain
preserving agents, solubilizers, stabilizing agents,
20 wetting agents, emulsifying agents, sweetening agents,
colouring agents, flavouring agents, salts for varying the
osmotic pressure, buffers, coating agents or antioxidants.
They can also contain still other therapeutically valuable
substances.

25 The invention also relates to pharmaceutical composi-
tions for the treatment or prevention of angina pectoris,
ischaemia, arrhythmias, high blood pressure and cardiac
insufficiency which comprise a compound of formula I and a
30 pharmaceutically inert, inorganic or organic excipient.

The invention also relates to a method for treating or
preventing angina pectoris, ischaemia, arrhythmias, high
blood pressure and cardiac insufficiency which comprises
35 administering an effective amount of a compound of formula
I to a warm-blooded animal in need of such treatment.

In accordance with the invention compounds of formula I can be used in the control or prevention of angina pectoris, ischaemia, arrhythmias, high blood pressure and cardiac insufficiency by administering an effective amount of a compound of formula I to a warm-blooded animal in need of such treatment. The dosage can vary within wide limits and will, of course, be adjusted to the individual requirements in each particular case. In general, in the case of oral administration a daily dosage of about 25 to 150 mg of a compound of formula I should be appropriate, whereby, however, the upper limit just given can also be exceeded when this is shown to be indicated.

The following Examples are intended to illustrate the invention, but they are not intended to be limiting in any manner. All temperatures are given in degrees Celsius.

Example 1

A mixture of 5.4 g (28.7 mmol) of 2-[3-(methylamino)-propyl]benzimidazole, 11.4 g (28.7 mmol) of 2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1 α -isopropyl-2 β -naphthyl)ethyl p-toluenesulphonate and 3.74 g (28.7 mmol) of Hünig base is heated to 120° for 30 minutes. The mixture is thereupon poured into ice-water and extracted with methylene chloride. After drying the organic phase over magnesium sulphate the solvent is evaporated and the residue is chromatographed on silica gel with a 6:1 mixture of methylene chloride and methanol as the elution agent. There are thus obtained 6.2 g (49%) of [1S,2S]-2-[2-[[3-(2-benzimidazolyl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol, $[\alpha]_{589}^{20} = +41.2^\circ$ (c = 0.8%; methanol).

The 2-[3-(methylamino)propyl]benzimidazole used as the starting material was prepared as follows:

22.8 g (91 mmol) of 4-[1-(benzyloxy)-N-methylform-
5 amido]butyric acid are dissolved in 200 ml of tetrahydro-
furan. The mixture is cooled and 13 ml (128 mmol) of tri-
ethylamine and 12 ml (91.5 mmol) of isobutyl chloroformate
are added dropwise thereto at -15°. After 2.5 hours 10.3 g
(95 mmol) of o-phenylenediamine in 85 ml of tetrahydro-
31 furan are added at -10° within 30 minutes. After stirring
31 at room temperature for 1 hour the solvent is evaporated
under reduced pressure. Thereupon, water is added and the
mixture is extracted with ethyl acetate. The organic phase
is washed with saturated aqueous sodium bicarbonate
15 solution and saturated aqueous sodium chloride solution.
After drying over magnesium sulphate and evaporation of
the solvent there are obtained 27.05 g of a product which
is chromatographed on silica gel with ethyl acetate as the
elution agent. There are thus obtained 20.1 g (71%) of
20 benzyl [3-[(2-aminophenyl)carbamoyl]propyl]methylcarba-
mate.

PM MS: M^+ 341.

20.1 g (59 mmol) of benzyl [3-[(2-aminophenyl)car-
25 bamoyl]propyl]methylcarbamate are dissolved in 450 ml of
toluene and treated with 7 g (37 mmol) of p-toluenesul-
phonic acid. The reaction mixture is thereafter heated to
reflux for 2 hours, whereby the water formed is removed
from the reaction mixture by means of a water separator.
30 After evaporation and dissolution of the residue in ethyl
acetate the solution is washed twice with saturated
aqueous sodium bicarbonate solution and twice with satu-
rated aqueous sodium chloride solution. The organic phase
is dried over magnesium sulphate and evaporated. Chromato-
35 graphy of the crude product on silica gel with ethyl
acetate as the elution agent yields 11 g (58%) of benzyl
14 [3-(2-benzimidazolyl)propyl]methylcarbamate, m.p. 83-86°.

11.0 g (34 mmol) of benzyl [3-(2-benzimidazolyl)-propyl]methylcarbamate are reduced with hydrogen in 150 ml of methanol in the presence of 2.5 g of palladium-on-carbon (5%) as the catalyst. There are thus obtained
5 5.45 g (85%) of 2-[3-(methylamino)propyl]benzimidazole, m.p. 134-136°.

Example 2

6.2 g (14.6 mmol) of [1S,2S]-2-[2-[[3-(2-benzimidazolyl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol are dissolved in 50 ml of chloroform. 2.5 ml (15 mmol) of N-ethyldiisopropylamine and 5 ml (55 mmol) of methoxyacetyl chloride are added
15 thereto at 0°. The reaction mixture is stirred at room temperature overnight and thereafter treated with 100 ml of 1N sodium hydroxide solution and extracted with chloroform. After drying over magnesium sulphate and evaporation of the solvent the residue is chromatographed on silica
20 gel with a 6:1 mixture of methylene chloride and methanol. There are thus obtained 6.2 g of an oil which are dissolved in 30 ml of ethanol and treated with 15 ml of ether saturated with hydrochloric acid. Thereupon, the reaction mixture is evaporated and the residue is crystallized from
25 ethanol/diethyl ether. There are thus obtained 5.4 g (65%) of [1S,2S]-2-[2-[[3-(2-benzimidazolyl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate dihydrochloride, m.p. 128°.

Example 3

A mixture of 4.2 g (10.35 mmol) of 2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1 α -isopropyl-2 β -naphthyl)ethyl p-toluenesulphonate and 4.5 g (20.7 mmol)
35 of 2-[5-(methylamino)pentyl]benzimidazole is heated to 100° for 30 minutes. Thereafter there are added firstly 100 ml of chloroform, then, after cooling, 100 ml of ether

and finally 100 ml of 1N aqueous hydrochloric acid. After stirring for 30 minutes the reaction mixture is made basic with concentrated aqueous sodium hydroxide solution and the organic phase is decanted off, dried and evaporated.

5 After chromatography on silica gel with a 6:1 mixture of methylene chloride and methanol there are obtained 2.7 g (58.2%) of [1S,2S]-2-[2-[[5-(2-benzimidazolyl)pentyl]-methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol, $[\alpha]_{589}^{20} = +36.8^\circ$ (c = 0.25; methanol).

10

Example 4

6 g (13.2 mmol) of [1S,2S]-2-[2-[[5-(2-benzimidazolyl)pentyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol, 20 ml of methoxyacetic anhydride and 1.05 g (13.3 mmol) of pyridine are heated to 70° while stirring. After 2 hours the mixture is cooled and treated with 500 ml of 3N sodium hydroxide solution and 500 ml of methylene chloride and stirred vigorously.

15

20 The organic phase is dried over magnesium sulphate and evaporated. The residue is dissolved in ethanol and treated with ether saturated with hydrochloric acid. After evaporation and crystallization from ethanol/ether there are obtained 6.2 g (78.5%) of [1S,2S]-2-[2-[[5-(2-benzimidazolyl)pentyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate dihydrochloride, m.p. 196-198°.

25

Example 5

The following compounds were prepared in an analogous manner to that described in Examples 1 and 3:

35 - starting from 2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1 α -isopropyl-2 β -naphthyl)ethyl p-toluene-sulphonate and 2-[4-(methylamino)butyl]benzimidazole

the [1S,2S]-2-[2-[[4-(2-benzimidazolyl)butyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol, MS: M^+ 437;

- 802
n
6062
- 5 - starting from 2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1 α -isopropyl-2 β -naphthyl)ethyl p-toluene-sulphonate and 2-[7-(methylamino)heptyl]benzimidazole the [1S,2S]-2-[2-[[7-(2-benzimidazolyl)heptyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol dihydrochloride, $[\alpha]_{589}^{20} = +32.9^\circ$ (c = 1%; methanol);
- 604
- 10

- 2
n
6062
- 15 - starting from 2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1 α -isopropyl-2 β -naphthyl)ethyl p-toluene-sulphonate and 2-[11-(methylamino)undecyl]benzimidazole the [1S,2S]-2-[2-[[11-(2-benzimidazolyl)-undecyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol;

- 602
n
6062
- 20 - starting from 2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1 α -isopropyl-2 β -naphthyl)ethyl p-toluene-sulphonate and 5,6-dimethyl-2-[7-(methylamino)heptyl]benzimidazole the [1S,2S]-2-[2-[[7-(5,6-dimethyl-2-benzimidazolyl)heptyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol, $[\alpha]_{589}^{20} = +33.6^\circ$ (c = 0.5%; methanol);
- 604
- 25

- 602
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6062
- 30 - starting from 2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1 α -isopropyl-2 β -naphthyl)ethyl p-toluene-sulphonate and 2-[5-(dodecylamino)pentyl]benzimidazole the [1S,2S]-2-[2-[[5-(2-benzimidazolyl)pentyl]dodecylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol, MS: M^+ 606;
- 604

- 602
n
6062
- 35 - starting from 2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1 α -isopropyl-2 β -naphthyl)ethyl p-toluene-sulphonate and 2-[7-(methylamino)heptyl]-1H-imidazo-
- 20

[4,5-c]pyridine the [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[[7-(1H-imidazo[4,5-c]pyridin-2-yl)heptyl]methylamino]ethyl]-2-naphthalenol, MS: M^+ 480.

5

The benzimidazole derivatives used as the starting materials were prepared in an analogous manner to that described in Example 1.

10

Example 6

The following compounds were prepared by methoxyacetylating the corresponding hydroxy derivatives in an analogous manner to that described in Examples 2 and 4:

15

- [1S,2S]-2-[2-[[4-(2-Benzimidazolyl)butyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate dihydrochloride,
[α]₅₈₉²⁰ = +28.6° (c = 1%; methanol);

20

- [1S,2S]-2-[2-[[7-(2-benzimidazolyl)heptyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate dihydrochloride,
[α]₅₈₉²⁰ = +25.4° (c = 1%; methanol);

25

- [1S,2S]-2-[2-[[11-(2-benzimidazolyl)undecyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate dihydrochloride,
[α]₅₈₉²⁰ = +23.7° (c = 1%; methanol);

30

- [1S,2S]-2-[2-[[7-(5,6-dimethyl-2-benzimidazolyl)heptyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate hydrochloride.
(1:1.85), [α]₅₈₉²⁰ = +26.5° (c = 1%; methanol);

35

- [1S,2S]-2-[2-[[5-(2-benzimidazolyl)pentyl]dodecylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-

-naphthyl methoxyacetate dihydrochloride.

$[\alpha]_{589}^{20} = +22.0^{\circ}$ (c = 0.25%; methanol);

- 5 - [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-
-[[7-(1H-imidazo[4,5-c]pyridin-2-yl)heptyl]methylamino]-
ethyl]-2-naphthyl methoxyacetate dihydrochloride. m.p.
112-115°.

Example 7

- 10 0.79 g (3.8 mmol) of 2-[3-(methylamino)propyl]benz-
thiazole, 1.54 g (3.8 mmol) of 2-(6-fluoro-1,2,3,4-tetra-
hydro-2-hydroxy-1 α -isopropyl-2 β -naphthyl)ethyl p-
-toluenesulphonate and 0.49 g (3.8 mmol) of Hünig base are
15 stirred at 120° for 2.5 hours. After cooling and dis-
solution of the precipitate with a small amount of methy-
lene chloride the reaction solution is chromatographed on
silica gel with a 12:1 mixture of methylene chloride and
methanol. There are thus obtained 1.12 g (76%) of [1S,2S]-
20 -2-[2-[[3-(2-benzthiazolyl)propyl]methylamino]ethyl]-6-
-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol,
MS: M⁺ 440.

- 25 The following compounds were prepared in an analogous
manner to that described above:

- 30 - starting from 2-(6-fluoro-1,2,3,4-tetrahydro-2-
-hydroxy-1 α -isopropyl-2 β -naphthyl)ethyl p-toluene-
sulphonate and 2-[5-(methylamino)pentyl]benzthiazole
the [1S,2S]-2-[2-[[5-(2-benzthiazolyl)pentyl]methyl-
amino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-
-naphthalenol, MS: M⁺ 468;

- 35 - starting from 2-(6-fluoro-1,2,3,4-tetrahydro-2-
-hydroxy-1 α -isopropyl-2 β -naphthyl)ethyl p-toluene-
sulphonate and 2-[7-(methylamino)heptyl]benzthiazole
the [1S,2S]-2-[2-[[7-(2-benzthiazolyl)heptyl]methyl-

amino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol, MS: M^+ 496.

The 2-[3-(methylamino)propyl]benzthiazole used as the starting material was prepared as follows:

5.0 g (19.9 mmol) of 4-[1-(benzyloxy)-N-methylformamido]butyric acid are dissolved in 175 ml of tetrahydrofuran. To the solution, cooled to -20° , are added 2.95 ml (2.1 g; 24 mmol) of triethylamine and 2.95 ml (22 mmol) of isobutyl chloroformate. The reaction mixture is thereafter stirred at this temperature for 1 hour. 2.45 g (19.6 mmol) of 2-aminothiophenol are then added and the reaction mixture is stirred at room temperature for 20 hours. Thereupon, 250 ml of water are added and the mixture is extracted with ethyl acetate. The organic phase is dried over magnesium sulphate and evaporated under reduced pressure. After chromatography on silica gel using a 1:1 mixture of ethyl acetate and hexane there are obtained 1.7 g (25.1%) of benzyl [3-(2-benzthiazolyl)propyl]methylcarbamate as an oil, MS: M^+ 340.

1.7 g (4.99 mmol) of benzyl [3-(2-benzthiazolyl)propyl]methylcarbamate are dissolved at 0° in 40% hydrogen bromide in acetic acid and stirred at room temperature for 20 hours. Thereupon, 60 ml of ether are added and, after 1.5 hours, the precipitate formed is filtered off. After washing the crystalline precipitate with ether and drying there are obtained 1.71 g (93.1%) of 2-[3-(methylamino)propyl]benzthiazole dihydrobromide, m.p. $196-197^\circ$.

The following compounds were prepared in an analogous manner to that described above:

- 2-[5-(methylamino)pentyl]benzthiazole, MS: M^+ 234;
2-[7-(methylamino)heptyl]benzthiazole, MS: M^+ 262.

Example 8

1.12 g (2.54 mmol) of [1S,2S]-2-[2-[[3-(2-benzthia-
zoly1)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-
1-isopropyl-2-naphthalenol are dissolved in 0.2 g of pyri-
dine. 5 ml of methoxyacetic anhydride are added thereto.
The reaction mixture is heated to 60° for 2 hours. There-
after, 100 ml of 1N sodium hydroxide solution are added
thereto at 0° and the mixture is extracted with 100 ml of
ethyl acetate. The organic phase is dried with magnesium
sulphate, filtered and evaporated under reduced pressure.
The residue is chromatographed on silica gel using a 30:1
mixture of methylene chloride and methanol. There is thus
obtained 0.9 g of an oily product which is dissolved in
ethyl acetate and treated with ether saturated with hydro-
chloric acid. After evaporation to 20 ml, 40 ml of ether
are added and the reaction mixture is stirred for 1 hour.
The separated precipitate is filtered off and dried. There
is thus obtained 0.9 g (64.5%) of [1S,2S]-2-[2-[[3-(2-
-benzthiazoly1)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-
-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate dihydro-
chloride, m.p. 130-134°.

The following compounds were prepared by methoxy-
acetylating the corresponding hydroxy derivatives in an
analogous manner to that described above:

- [1S,2S]-2-[2-[[5-(2-Benzthiazoly1)pentyl]methylamino]-
ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-
-naphthyl methoxyacetate hydrochloride (5:8),
[α]₅₈₉⁽²⁰⁾ = +27.4° (c = 0.5%; methanol);
- [1S,2S]-2-[2-[[7-(2-benzthiazoly1)heptyl]methylamino]-
ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-
-naphthyl methoxyacetate hydrochloride (4:5),
[α]₅₈₉⁽²⁰⁾ = +25.8° (c = 1%; methanol).

Example 9

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5 In an analogous manner to that described in Examples 1 and 4, starting from (S)-6-[1-(benzyloxy)-N-methylformamido]heptanoic acid via [1S,2S]-2-[2-[[[(S)-5-(2-benzimidazolyl)-1-methylpentyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol there was prepared [1S,2S]-2-[2-[[[(S)-5-(2-benzimidazolyl)-1-methylpentyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate dihydro-10 chloride, $[\alpha]_{589}^{20} = +20.0^\circ$ (c = 0.7%; methanol).

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The (S)-6-[1-(benzyloxy)-N-methylformamido]heptanoic acid used as the starting material was prepared as follows:

15 200 g (1.39 mol) of 6-oxoheptanoic acid are dissolved in 1.2 l of methylene chloride. 14 ml of concentrated sulphuric acid are added thereto at -20° . 0.6 l (6.3 mol) of isobutylene is then condensed at -40° and thereupon 20 left to distill into the reaction flask. Thereafter, the reaction mixture is left to react for 6 days at room temperature under the reflux of the reagent. Thereafter, one litre of saturated aqueous sodium bicarbonate solution is added thereto while stirring. The aqueous phase is 25 extracted with methylene chloride. The combined organic phases are dried over magnesium sulphate and evaporated under reduced pressure. There are thus obtained 268.0 g (1.338 mol; 96.4%) of tert.-butyl 6-oxoheptanoate, which are heated to reflux for 12 hours together with 162.1 g 30 (1.338 mol) of (S)-(-)-1-phenylethylamine and 5.8 g (30.5 mmol) of p-toluenesulphonic acid in 1.9 l of toluene with the simultaneous separation of water. After evaporation of the solvent there are obtained 395.5 g (1.3 mol; 97.4%) of tert.butyl (E/Z)-6-[[[(R)- α -methylbenzyl]-35 imino]heptanoate which are dissolved in 7 l of methanol. 43 g of Raney-nickel are added thereto and the mixture is hydrogenated at 10 bar for 24 hours. Thereafter, the

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mixture is filtered and the solution is evaporated. The
resulting 378.5 g of oil are dissolved in 1.1 l of
ethylacetate and treated at 0° with 130 ml of 10N
ethanolic hydrochloric acid. After stirring at 0° for
5 1 hour the crystals formed are filtered off and dried. By
three-fold recrystallization of the resulting 282 g of
crystals from ethyl acetate there are obtained 172.7 g
(38.9%) of tert.butyl (S)-6-[[[(S)- α -methylbenzyl]amino]-
hexanoate hydrochloride, m.p. 154-156°.

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160 g (0.648 mol) of the above hydrochloride are
dissolved in 2.4 l of ethanol and hydrogenated at 10 bar
in the presence of 20 g of palladium-on-carbon (5%). After
filtering off the catalyst the solvent is evaporated and
15 the residue is crystallized from 560 ml of ethyl acetate
and 240 ml of hexane. There are thus obtained 101 g
(90.8%) of tert.-butyl (S)-6-aminoheptanoate hydro-
chloride, m.p. 107-109°.

20 89 g (374 mmol) of tert.butyl (S)-6-aminoheptanoate
hydrochloride are dissolved in 1.3 l of methylene
chloride. The solution is saturated with hydrogen chloride
and heated to reflux for 4 hours. After filtering off and
drying the precipitate formed there are obtained 60.8 g
25 (89.5%) of (S)-6-aminoheptanoic acid hydrochloride, m.p.
157-160°.

30 To 30 g (166 mmol) of (S)-6-aminoheptanoic acid hydro-
chloride in 57 ml of water are added 57 ml of 4N aqueous
sodium hydroxide solution and thereafter dropwise simul-
taneously at 10° 92 ml of 4N aqueous sodium hydroxide
solution and 42 ml (294 mmol) of benzyl chloroformate so
that the pH value always lies between 10 and 12. After the
precipitation of the product the mixture is stirred at 0°
35 for a further 2 hours. Thereafter, 300 ml of water are
added and the reaction mixture is extracted with ether.
The aqueous phase is then acidified with 20 ml of concen-

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trated hydrochloric acid and extracted with methylene chloride. The methylene chloride phase is dried over magnesium sulphate and evaporated. The crystals obtained are recrystallized from chloroform/hexane, whereby there
5 are obtained 33.1 g (72%) of (S)-6-[1-(benzyloxy)-formamido]heptanoic acid, m.p. 82-83°.

6.5 g (23 mmol) of (S)-6-[1-(benzyloxy)formamido]-heptanoic acid are added to a suspension of 3.05 g of 55%
10 sodium hydride (70 mmol) in 200 ml of dimethylformamide and the mixture is left to react at 40° for 30 minutes. Thereafter, 13 g (90 mmol) of methyl iodide are added dropwise and the reaction mixture is heated to 70° for 1 hour. After evaporation of the solvent 120 ml of 1N
15 aqueous sodium hydroxide solution and 120 ml of ethanol are added and the reaction mixture is heated to reflux for 30 minutes. Thereafter, the mixture is evaporated to half, 100 ml of saturated aqueous sodium bicarbonate solution are added and the mixture is extracted with ethyl acetate.
20 The aqueous phase is acidified and extracted with methylene chloride. The organic phase is dried over magnesium sulphate and evaporated. The residue (5 g) is chromatographed on silica gel with a 12:1 mixture of methylene chloride and methanol, whereby there are
25 obtained 3.5 g (52.2%) of (S)-6-[1-(benzyloxy)-N-methylformamido]heptanoic acid, MS: M⁺ 293.

Example 10

30 A mixture of 1.4 g (3.33 mmol) of 2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-methoxy-2-naphthyl]-ethyl p-toluenesulphonate and 1.63 g (6.66 mmol) of 2-[7-(methylamino)heptyl]benzimidazole is heated to 100° for 30 minutes. The mixture is thereafter poured into 100 ml
35 of water and extracted with 100 ml of ethyl acetate. The organic phase is dried over magnesium sulphate and evaporated under reduced pressure, and the residue is chromato-

graphed on silica gel with a 6:1 mixture of methylene chloride and methanol. There is thus obtained a yellowish oil (1 g) which is dissolved in 20 ml of ethanol and treated with 2 ml of ether saturated with hydrochloric acid. The mixture is then evaporated under reduced pressure and the residue is crystallized from ethyl acetate/ethanol/ether and dried, whereby there is obtained 0.7 g (37.2%) of [1S,2S]-2-[2-[[7-(2-benzimidazolyl)-heptyl]methylamino]ethyl]-6-fluoro -1,2,3,4-tetrahydro-1-isopropyl-2-methoxynaphthalenol dihydrochloride, m.p. 179-181°.

The 2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-methoxy-2-naphthyl]ethyl p-toluenesulphonate used as the starting material was prepared as follows:

2062 ✓ A mixture of 5.04 g (20 mmol) of 6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1 α -isopropyl-2 β -naphthylethanol, 6.13 g (22 mmol) of triphenylchloromethane and 50 ml of pyridine is stirred at room temperature for 20 hours. The reaction mixture is thereafter poured into 500 ml of ice-water and extracted with 400 ml of ether. The ether extracts are washed with 400 ml of 1N aqueous hydrochloric acid, 400 ml of saturated aqueous sodium bicarbonate solution and 400 ml of water. After drying over magnesium sulphate the ether is evaporated under reduced pressure. There are obtained 8.25 g (83%) of [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-(trityloxy)ethyl]-2-naphthalenol. 8 g (16.2 mmol) of this compound are dissolved in 300 ml of tetrahydrofuran and treated at -20° with 35.6 mmol of freshly prepared lithium diisopropylamide. Thereafter, 9.2 g (64.8 mmol) of methyl iodide are added and the reaction mixture is stirred at room temperature for 20 hours. The reaction mixture is poured into ice-water and extracted with methylene chloride. The organic phase is dried over magnesium sulphate and the solvent is evaporated under reduced pressure. After

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chromatography on silica gel using a 1:2 mixture of methylene chloride and hexane and recrystallization from hexane there are obtained 4.15 g (54.7%) of [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-methoxy-2-[2-(trityloxy)ethyl]naphthalenol, m.p. 132-134°.

4.15 g (8.16 mmol) of the above compound are left to stand at 0° for 2 hours with 15 ml of ether saturated with hydrochloric acid. After evaporation of the solvent and chromatography of the residue on silica gel using a 1:2 mixture of ethyl acetate and hexane there is obtained 1.0 g (47%) of [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-methoxy-2-naphthylethanol, $[\alpha]_{589}^{20} = +65.6^\circ$ (c = 0.25%; methanol).

0.98 g (3.7 mmol) of [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-methoxy-2-naphthylethanol is dissolved in 6 ml of pyridine and left to react at 0° for 1 hour with 1.06 g (5.6 mmol) of toluene-4-sulphochloride. The reaction mixture is thereafter poured into 100 ml of water and extracted with 200 ml of ether. The ether extract is washed with 100 ml of 1N aqueous hydrochloric acid, 100 ml of saturated aqueous sodium bicarbonate solution and 100 ml of water. After drying the ethereal solution over magnesium sulphate and evaporation of the solvent there are obtained 1.50 g (97.4%) of 2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-methoxy-2-naphthyl]ethyl p-toluenesulphonate, $[\alpha]_{589}^{20} = +42.6$ (c = 0.5%; methanol).

Example 11

2.0 g (4.43 mmol) of [1S,2S]-2-[2-[[5-(2-benzimidazolyl)pentyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol dissolved in 30 ml of tetrahydrofuran are added to a suspension of 436 mg (10 mmol) of 55% sodium hydride in 20 ml of tetrahydro-

furan. After stirring at room temperature for 45 minutes 1.42 g (10 mmol) of methyl iodide are added thereto. After a further hour, water and methylene chloride are added and the reaction mixture is shaken vigorously. The organic
5 phase is dried over magnesium sulphate and evaporated. The residue is chromatographed on silica gel with a 6:1 mixture of methylene chloride and methanol, whereby there are obtained 1.2 g (60%) of [1S,2S]-6-fluoro-1,2,3,4-tetra-
hydro-1-isopropyl-2-[2 -[methyl-[5-(1-methyl-2-benzimi-
10 dazolyl)pentyl]amino]ethyl]-2 -naphthalenol, MS: M^+ 465.

[1S,2S]-2-[2-[[7-(1-Dodecyl-2 -benzimidazolyl)heptyl]-
methylamino]ethyl]-6-fluoro-1,2,3,4 -tetrahydro-1-iso-
propyl-2-naphthalenol was prepared in analogous manner to
15 that described above by reaction with dodecyl iodide.

Example 12

A mixture of 1.2 g (2.58 mmol) of [1S,2S]-6-fluoro-
20 -1,2,3,4-tetrahydro-1 -isopropyl-2-[2-[methyl-[5-(1-
-methyl-2 -benzimidazolyl)pentyl]amino]ethyl]-2-naphthal-
enol, 206 mg (2.6 mmol) of pyridine and 4 ml of
methoxyacetic anhydride is heated to 70° for 2 hours.
Thereafter, 100 ml of 3N aqueous sodium hydroxide solution
25 are added thereto and the mixture is extracted with 100 ml
of methylene chloride. The organic phase is dried over
magnesium sulphate and evaporated. The product is
chromatographed on silica gel using a 15:1 mixture of
methylene chloride and methanol. The resulting 550 mg of
30 oil are dissolved in 50 ml of ethyl acetate and treated
with 1 ml of ether saturated with hydrochloric acid. After
evaporation of the solvent the residue is crystallized
from ethyl acetate/ether, whereby there are obtained
600 mg (41%) of [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-
35 -isopropyl-2-[2-[methyl-[5-(1-methyl-2 -benzimidazolyl)-
pentyl]amino]ethyl]-2-naphthyl methoxyacetate dihydro-
chloride, m.p. 203-205°.

[1S,2S]-2-[2-[[7-(1-Dodecyl-2-benzimidazolyl)heptyl]-methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate dihydrochloride,

$[\alpha]_{589}^{20} = +20.4^\circ$ (c = 0.9%; methanol), was prepared in an analogous manner to that described above.

Example 13

0.425 g (1 mmol) of [1S,2S]-2-[2-[[3-(2-benzimidazolyl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate is dissolved in 60 ml of methanol and subsequently treated with 10 ml of 6% hydrogen peroxide and 50 mg (0.15 mmol) of sodium tungstate. After stirring at room temperature for 20 hours 100 mg of platinum-on-carbon (5%) in 2 ml of water are added thereto and the mixture is stirred for a further hour. Thereupon, the mixture is filtered, the filtrate is concentrated, the residue is diluted with a small amount of methylene chloride and the mixture is chromatographed on silica gel with a 15:1 mixture of methylene chloride and methanol as the elution agent. There are thus obtained 0.18 g (35.2%) of a first diastereomer of [1S,2S]-2-[2-[[3-(2-benzimidazolyl)propyl]methyl-N-oxidoamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate with a R_f value of 0.33, $[\alpha]_{589}^{20} = +39.4^\circ$ (c = 0.5%; methanol), and 0.276 g (54%) of a second diastereomer of the named compound with a R_f value of 0.26 (methylene chloride/methanol 6:1), $[\alpha]_{589}^{20} = +34.8^\circ$ (c = 0.5%; methanol).

Example 14

5.0 g (12.3 mmol) of 2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1 α -isopropyl-2 β -naphthyl)ethyl p-toluenesulphonate and 4.0 g (24.6 mmol) of 2-methylaminobenzthiazole are heated to 120° for 30 minutes. Thereafter, 50 ml of a 12:1 mixture of methylene chloride and methanol are added

and the reaction mixture is purified by column chromatography on silica gel using a 1:1 mixture of hexane and ethyl acetate as the elution agent. In this manner there are obtained 3.22 g (65.7%) of [1S,2S]-2-[2-[(2-benzthiazolyl)methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthalenol, m.p. 102-103°.

Example 15

6.1 g (15 mmol) of [1S,2S]-2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl)ethyl p-toluenesulphonate and 6.8 g (30 mmol) of 1-[2-(methylamino)ethyl]-2-benzimidazolinone hydrochloride are stirred at 130° for 4.5 hours in a mixture of 30 ml of dimethylformamide and 30 ml of N-ethyldiisopropylamine. The reaction mixture is poured into 600 ml of ice-water and extracted with 700 ml of methylene chloride. The extract is washed with water, dried over potassium carbonate and evaporated. The thus-obtained product is chromatographed on 150 g of silica gel with methylene chloride and 0-10% isopropanol as the elution agent, whereby 5.2 g (72%) of 1-[2-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]methylamino]ethyl]-2-benzimidazolinone are obtained as an oil.

The 1-[2-(methylamino)ethyl]-2-benzimidazolinone hydrochloride used as the starting material was prepared as follows:

93.8 ml (150 mmol) of a n-butyllithium solution (about 1.6M in hexane) are added dropwise at 0-5° to 24.8 g (150 mmol) of 2-(N-benzyl-N-methylamino)ethanol dissolved in 250 ml of absolute tetrahydrofuran. After stirring at 0° for 15 minutes 11.7 ml (150 mmol) of methanesulphochloride in 50 ml of tetrahydrofuran are added dropwise at a temperature between 0 and 5° and the reaction mixture is stirred at 0° for 30 minutes.

5.8 g (133 mmol) of a 55% sodium hydride dispersion in mineral oil are washed oil-free with hexane and suspended in 40 ml of dimethylformamide. 23.1 g (132.5 mmol) of 1-(1-methylvinyl)benzimidazolin-2-one in 90 ml of dimethylformamide are subsequently added dropwise at room temperature and the reaction mixture is stirred for a further 15 minutes.

This reaction mixture is added dropwise at 0° to the reaction solution described above. Thereafter, the mixture is heated to 70° and stirred for 3 hours. The reaction mixture is subsequently poured into 1 l of ice-water and extracted with 600 ml of methylene chloride. The extract is washed with water, dried over potassium carbonate and evaporated. The thus-obtained product is chromatographed on 500 g of silica gel with methylene chloride and 0-5% isopropanol as the elution agent, whereby there are obtained 26.8 g (63%) of 1-(1-methylvinyl)-3-[2-(N-benzyl-N-methylamino)ethyl]-2-benzimidazolinone as an oil.

26.5 g (82.5 mmol) of the above-named compound are dissolved in 265 ml of ethanol, treated with 26.5 ml of concentrated aqueous hydrochloric acid while stirring and heated to reflux for 1 hour. After cooling the reaction mixture to 5°, 1-[2-(N-benzyl-N-methylamino)ethyl]-2-benzimidazolinone crystallizes out in the form of the hydrochloride, m.p. 107-109°; yield 24.2 g (92%).

22.9 g (72 mmol) of 1-[2-(N-benzyl-N-methylamino)-ethyl]-2-benzimidazolinone hydrochloride are dissolved in 250 ml of methanol, treated with 2.5 g of palladium-on-carbon (10%) and hydrogenated at room temperature for 90 minutes. The residue obtained after filtration and concentration is recrystallized from methanol/ether, whereby there are obtained 15.5 g (94%) of 1-[2-(methylamino)ethyl]-2-benzimidazolinone hydrochloride, m.p. 177-180°.

Example 16

4.57 g (10.7 mmol) of 1-[2-[[2-[[1S,2S]-6-fluoro-
-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]-
5 ethyl]methylamino]ethyl]-2-benzimidazolinone are dissolved
in 15 ml of methylene chloride, treated with 2.2 ml of
pyridine and 7.0 g (43 mmol) of methoxyacetic anhydride
and stirred at room temperature for 20 hours. Thereafter,
the mixture is treated with 30 ml of 3N sodium hydroxide
10 solution while cooling with ice and stirred at room
temperature for 15 minutes. The reaction mixture is
subsequently poured into 400 ml of ice-water and extracted
with 600 ml of methylene chloride. The extract is washed
with water, dried over potassium carbonate and con-
15 centrated. There are thus obtained 6.9 g of an oil (N,O-
-diacylated product) which are dissolved in 30 ml of
methanol and treated at room temperature with 11.5 ml of
1N aqueous sodium hydroxide solution. After stirring for
30 minutes the mixture is poured into 400 ml of ice-water
20 and extracted with 600 ml of methylene chloride. The
extract is washed with water, dried over potassium
carbonate, evaporated, treated with one equivalent of
hydrochloric acid in methanol, again evaporated and
finally recrystallized from methanol/ether. There are thus
25 obtained 3.9 g (72%) of [1S,2S]-6-fluoro-1,2,3,4-tetra-
hydro -1-isopropyl-2-[2-[methyl-[2-(2-oxo-1-benz-
imidazoliny]ethyl]amino]ethyl]-2-naphthyl methoxyacetate
hydrochloride, m.p. 130-133° (dec.); $[\alpha]_D^{20} = +26.0^\circ$
(c = 1%; methanol).

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Example 17

In analogy to Example 15, by reacting [1S,2S]-2-(6-
-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-
35 -naphthyl)ethyl p-toluenesulphonate with 1-[6-(methyl-
amino)hexyl]-2-benzimidazolinone there was obtained 1-[6-
-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-

-isopropyl-2-naphthyl]ethyl]methyamino]hexyl]-2-benzimidazolinone as an oil.

The 1-[6-(methyamino)hexyl]-2-benzimidazolinone used
5 as the starting material was prepared as follows:

17.6 g (150 mmol) of 6-amino-1-hexanol dissolved in
50 ml of methanol are added dropwise at room temperature
to 32.7 g (150 mmol) of di-tert.-butyl dicarbonate in
10 100 ml of methanol. After stirring at room temperature for
4 hours the reaction mixture is evaporated, whereby there
are obtained 36.6 g of tert.-butyl (6-hydroxyhexyl)-
carbamate as an oil which is used directly in the next
step.

15 34.8 g of tert.-butyl (6-hydroxyhexyl)carbamate are
dissolved in 250 ml of methylene chloride and treated at
0° with 24.0 ml (174 mmol) of triethylamine. Subsequently,
12.9 ml (166 mmol) of methanesulphochloride in 50 ml of
31 20 methylene chloride are added dropwise at -60° within 15
minutes and the reaction mixture is subsequently stirred
at -60° for 90 minutes. Thereafter, the reaction solution
is poured into 600 ml of ice-water and extracted with
800 ml of methylene chloride. The organic extract is
25 washed with water, dried over magnesium sulphate and
evaporated. There are thus obtained 58.6 g of tert.-butyl
[6-[(methyisulphonyl)oxy]hexyl]carbamate as an oil which
is processed without purification.

30 5.9 g (135 mmol) of a 55% sodium hydride dispersion in
mineral oil are washed oil-free with hexane and sub-
sequently covered with 100 ml of dimethylformamide. To
this suspension are added dropwise at room temperature
22.3 g (128 mmol) of 1-(1-methylvinyl)benzimidazolin-2-
35 -one in 100 ml of dimethylformamide. After stirring at
room temperature for 2 hours 55.0 g of tert.-butyl [6-
-[(methyisulphonyl)oxy]hexyl]carbamate in 100 ml of

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dimethylformamide are added dropwise and the reaction mixture is stirred at room temperature for 18 hours. Thereafter, the reaction mixture is poured into 1 l of water and extracted with 750 ml of methylene chloride. The organic extract is washed with water, dried over potassium carbonate and evaporated. The thus-obtained residue is chromatographed on 950 g of silica gel with methylene chloride/hexane, methylene chloride and a 95:5 mixture of methylene chloride and isopropanol as the elution agent, whereby there are obtained 45.3 g of tert.-butyl [6-[3-(1-methylvinyl)-2-oxo-1-benzimidazoliny]hexyl]carbamate as an oil.

5.3 g (121 mmol) of a 55% sodium hydride dispersion in mineral oil are washed oil-free with hexane and subsequently covered with 100 ml of dimethylformamide. To this suspension are added dropwise at room temperature 45.0 g (121 mmol) of tert.-butyl [6-[3-(1-methylvinyl)-2-oxo-1-benzimidazoliny]hexyl]carbamate and the reaction mixture is stirred at this temperature for 90 minutes. Subsequently, 9.0 ml (155 mmol) of methyl iodide in 50 ml of dimethylformamide are added dropwise at 10° and the reaction mixture is stirred at 10° for 1 hour and at room temperature for 16 hours. Thereafter, the reaction solution is poured into 800 ml of ice-water and extracted with 600 ml of methylene chloride. The extract is washed with water, dried over potassium carbonate and evaporated. The thus-obtained residue is chromatographed on 500 g of silica gel with hexane/ethyl acetate (4:1 and 1:1), whereby there are obtained 39.1 g of tert.-butyl methyl [6-[3-(1-methylvinyl)-2-oxo-1-benzimidazoliny]hexyl]carbamate as an oil.

38.8 g (100 mmol) of the last-named compound are dissolved in 300 ml of absolute ethanol, treated while stirring with 40 ml of concentrated aqueous hydrochloric acid and heated to reflux for 75 minutes. After cooling to

40° the reaction mixture is concentrated under reduced pressure and poured into 500 ml of ice-water. The aqueous phase is adjusted to pH 8-9 by the addition of concentrated aqueous ammonia solution and extracted with 600 ml of methylene chloride. The extract is washed with water and subsequently discarded. The combined aqueous phases are adjusted to pH 10-11 with 3N aqueous sodium hydroxide solution and extracted six times with 150 ml of methylene chloride/isopropanol (4:1) each time. The combined extracts are dried over potassium carbonate and evaporated, whereby there are obtained 21.6 g of 1-[6-(methylamino)hexyl]-2-benzimidazolinone as an oil.

Example 18

In analogy to Example 17, by reacting [1S,2S]-2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl)ethyl p-toluenesulphonate and 1-methyl-3-[6-(methylamino)hexyl]-2-benzimidazolinone there is obtained 1-[6-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]methylamino]hexyl]-3-methyl-2-benzimidazolinone as an oil.

The 1-methyl-3-[6-(methylamino)hexyl]-2-benzimidazolinone used as the starting material was prepared as follows:

A solution of 9.7 g (44.5 mmol) of di-tert.-butyl dicarbonate in 50 ml of methanol is added dropwise at room temperature to 10.0 g (40.4 mmol) of 1-[6-(methylamino)hexyl]-2-benzimidazolinone in 150 ml of methanol and the reaction mixture is stirred at room temperature for 16 hours. Thereafter, 6.9 ml (49.5 mmol) of triethylamine and a further 9.7 g of di-tert.-butyl dicarbonate in 50 ml of methanol are added and the mixture is stirred at room temperature for a further 16 hours. Thereafter, the reaction mixture is poured into 200 ml of water and

extracted with 400 ml of methylene chloride. The extracts are washed with water, dried over potassium carbonate and evaporated, whereby there are obtained 14.1 g of tert.-butyl methyl [6-(2-oxo-1-benzimidazoliny)hexyl]-carbamate as an oil.

2.6 g (59.6 mmol) of a 55% sodium hydride dispersion in mineral oil are washed oil-free with hexane and subsequently covered with 30 ml of dimethylformamide. To this suspension are added dropwise at room temperature within 20 minutes 13.8 g (39.7 mmol) of tert.-butyl methyl [6-(2-oxo-1-benzimidazoliny)hexyl]carbamate in 90 ml of dimethylformamide. After stirring at room temperature for 90 minutes, 6.2 ml (99.3 mmol) of methyl iodide in 30 ml of dimethylformamide are added dropwise at room temperature and the reaction mixture is stirred at this temperature for a further 16 hours. For the work-up, the mixture is poured into 200 ml of water and extracted with 300 ml of methylene chloride. The methylene chloride extract is washed with water, dried over potassium carbonate and concentrated. The residue is chromatographed on 110 g of silica gel with methylene chloride and methylene chloride/isopropanol (99:1 and 98:2), whereby there are obtained 9.0 g of tert.-butyl methyl [6-(3-methyl-2-oxo-1-benzimidazoliny)hexyl]carbamate as an oil.

In analogy to Example 17, last paragraph, from the compound obtained above there was obtained 1-methyl-3-[6-(methylamino)hexyl]-2-benzimidazolinone as an oil.

Example 19

In an analogous manner to that described in Example 17, by reacting [1S,2S]-2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl)ethyl p-toluenesulphonate and 1-[p-[4-(methylamino)butyl]phenyl]imidazole there was obtained [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-

-2-[2-[[4 -[p-(imidazol-1-yl)phenyl]butyl]methylamino]-ethyl]-2 -naphthalenol as an oil.

The 1-[p-[4-(methylamino)butyl]phenyl]imidazole used
5 as the starting material was prepared as follows:

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10 a) 53.1 g (116 mmol) of [2-(m-dioxan-2-yl)ethyl]tri-phenylphosphonium bromide are suspended in 160 ml of tetrahydrofuran and treated at -25° within 15 minutes with
15 77.3 ml (116 mmol) of n-butyllithium solution (about 1.5M in hexane). Thereafter, the mixture is stirred at -25° for 15 minutes. Subsequently, 10 ml of a mixture of tetrahydrofuran and 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrimidinone (1:1) are added, the mixture is stirred at
20 -25° for a further 5 minutes and then treated within 30 minutes at -25° with 20 g (116 mmol) of p-(imidazol-1-yl)-benzaldehyde in 150 ml of tetrahydrofuran/1,3-dimethyl-3,4,5,6 -tetrahydro-2-(1H)-pyrimidinone (1:1). After completion of the addition the reaction mixture is warmed
25 to room temperature and stirred at this temperature for 15 minutes. Thereafter, the reaction mixture is poured into 1 l of ice-water and extracted with 600 ml of methylene chloride. The methylene chloride extract is washed with water, dried over magnesium sulphate and evaporated. There
30 are thus obtained 42.2 g of a semi-crystalline product which is dissolved in 600 ml of methanol and hydrogenated exhaustively in the presence of 18 g of palladium-on-carbon (5%). After filtering off the catalyst and evaporation of the filtrate there are obtained 36.6 g of a
35 semi-crystalline residue which, in turn, is dissolved in 700 ml of methanol, treated with 22.4 g of p-toluene-sulphonic acid monohydrate and heated to reflux for 2.5 hours. After cooling to room temperature the pH value is adjusted to 7 with 36 g of sodium carbonate, the reaction mixture is evaporated, the residue is poured into 500 ml of water and extracted with 600 ml of methylene chloride. The methylene chloride extract is washed with water and

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saturated sodium chloride solution, dried over magnesium sulphate and evaporated, whereby there are obtained 36.1 g of a semi-crystalline residue. This is dissolved in 400 ml of tetrahydrofuran, treated with 110 ml of 3N aqueous hydrochloric acid, stirred at room temperature for 3 hours and subsequently concentrated under reduced pressure. Thereafter, the reaction mixture is poured into 500 ml of ice-water and extracted three times with 200 ml of ether each time. The aqueous phase is subsequently adjusted to pH 9 with potassium carbonate and extracted with 600 ml of methylene chloride. The methylene chloride extract is washed with water, dried over potassium carbonate and evaporated. The residue is chromatographed on 240 g of silica gel with methylene chloride and 0-5% isopropanol as the elution agent. There are thus obtained 13.2 g (53%) of 4-[p-(imidazol-1-yl)phenyl]butanal as an oil.

b) 37.8 g (558 mmol) of methylamine hydrochloride are dissolved in 200 ml of methanol and thereupon treated with 45.8 g (558 mmol) of sodium acetate and 3.9 g (62.1 mmol) of sodium cyanoborohydride. The reaction mixture is stirred at room temperature for 15 minutes and thereafter 12.05 g (56.24 mmol) of 4-[p-(imidazol-1-yl)phenyl]-butanal in 40 ml of methanol are added dropwise at room temperature within 15 minutes and the reaction mixture is stirred at room temperature for 3 hours. Thereafter, the reaction mixture is concentrated under reduced pressure, the residue is poured into 1 l of ice-water and extracted with 800 ml of methylene chloride. The organic extract is washed with water, dried over magnesium sulphate and evaporated. The residue obtained is chromatographed on 100 g of silica gel with methylene chloride/isopropanol/ aqueous, 25% ammonia (160:40:1 and 7:3:0.3, respectively), whereby there are obtained 3.8 g (29%) of 1-[p-[4-(methylamino)butyl]phenyl]imidazole as an oil.

Example 20

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P
5 In an analogous manner to that described in Example 15, by reacting [1S,2S]-2-(6-fluoro-1,2,3,4-tetrahydro-2--hydroxy-1-isopropyl-2-naphthyl)ethyl p-toluenesulphonate and 1-[4-(methylamino)butyl]-2-benzimidazolinone there was obtained 1-[4-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]methylamino]butyl]-2-benzimidazolinone as an oil.

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The 1-[4-(methylamino)butyl]-2-benzimidazolinone used as the starting material was prepared as follows:

15 In analogy to Example 17, from 4-(methylamino)-1-butanol there was obtained tert.-butyl methyl [4-[(methylsulphonyl)oxy]butyl]carbamate as an oil which was then converted into tert.-butyl methyl [4-[3-(1-methylvinyl)-2-oxo-1-benzimidazoliny]butyl]carbamate. This compound, likewise obtained as an oil, was then
20 converted, again in analogy to Example 17, into 1-[4-(methylamino)butyl]-2-benzimidazolinone which was again obtained as an oil.

Example 21

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✓
P
30 In an analogous manner to that described in Example 17, by reacting [1S,2S]-2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl)ethyl p-toluenesulphonate and 1-isopropyl-3-[4-(methylamino)butyl]-2-benzimidazolinone there was obtained 1-[4-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]methylamino]butyl]-3-isopropyl-2-benzimidazolinone as an oil.

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The 1-isopropyl-3-[4-(methylamino)butyl]-2-benzimidazolinone used as the starting material was prepared as follows:

8.14 g (22.6 mmol) of tert.-butyl methyl [4-[3-(1-methylvinyl)-2-oxo-1-benzimidazoliny]butyl]carbamate are dissolved in 80 ml of methanol and, after the addition of 1.6 g of palladium-on-carbon (5%), hydrogenated for 4 hours. Thereupon, the reaction mixture is filtered and evaporated, whereby there are obtained 8.5 g of tert.-butyl methyl [4-(3-isopropyl-2-oxo-1-benzimidazoliny)-butyl]carbamate as an oil. This is converted in analogy to the last paragraph of Example 17 into 1-isopropyl-3-[4-(methylamino)butyl]-2-benzimidazolinone which is likewise obtained as an oil.

Example 22

In an analogous manner to that described in Example 17, by reacting [1S,2S]-2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl)ethyl p-toluenesulphonate and 1-butyl-3-[6-(methylamino)hexyl]-2-benzimidazolinone there was obtained 1-[6-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]methylamino]hexyl]-3-butyl-2-benzimidazolinone as an oil.

The 1-butyl-3-[6-(methylamino)hexyl]-2-benzimidazolinone used as the starting material was prepared as follows:

In analogy to Example 18, from tert.-butyl methyl [6-(2-oxo-1-benzimidazoliny)hexyl]carbamate and butyl iodide there was obtained tert.-butyl methyl [6-(3-butyl-2-oxo-1-benzimidazoliny)hexyl]carbamate as an oil. This compound was converted in analogy to Example 17 into 1-butyl-3-[6-(methylamino)hexyl]-2-benzimidazolinone which was likewise obtained as an oil.

Example 23

In an analogous manner to that described in Example

17, by reacting [1S,2S]-2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl)ethyl p-toluenesulphonate and 1-(2-morpholinoethyl)-3-[6-(methylamino)hexyl]-2-benzimidazolinone there was obtained 1-[6-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]methylamino]hexyl]-3-(2-morpholinoethyl)-2-benzimidazolinone as an oil.

The 1-(2-morpholinoethyl)-3-[6-(methylamino)hexyl]-2-benzimidazolinone used as the starting material was prepared as follows:

9.0 g (25.9 mmol) of tert.-butyl methyl [6-(2-oxo-1-benzimidazoliny]hexyl]carbamate are dissolved in 250 ml of methanol and treated with 35 g (259 mmol) of potassium carbamate, 0.5 g of potassium iodide and portionwise with 16.9 g (90.6 mmol) of chloroethylmorpholine hydrochloride. Thereafter, the reaction mixture is heated to reflux for 16 hours. After cooling the reaction mixture is poured into 1 l of ice-water and extracted with 800 ml of methylene chloride. The extract is washed with water, dried and concentrated. The residue is dissolved in 50 ml of ether and extracted in each case once with 15 ml and 5 ml of 3N methanesulphonic acid in water and once with 5 ml of water. The combined aqueous phases are adjusted to pH 8-9 with ammonia and extracted three times with 100 ml of methylene chloride each time. The combined extracts are washed with water, dried over potassium carbonate and evaporated, whereby there are obtained 7.8 g (65.4%) of tert.-butyl methyl [6-[3-(2-morpholinoethyl)-2-oxo-1-benzimidazoliny]hexyl]carbamate as an oil.

This was then converted, likewise in analogy to Example 17, into 1-(2-morpholinoethyl)-3-[6-(methylamino)-hexyl]-2-benzimidazolinone dihydrochloride, m.p. 229-232°.

Example 24

W/C
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✓
In an analogous manner to that described in Example 17, by reacting [1S,2S]-2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl)ethyl p-toluenesulphonate and 1-benzyl-3-[4-(methylamino)butyl]-2-benzimidazolinone there was obtained 1-benzyl-3-[4-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]methylamino]butyl]-2-benzimidazolinone as an oil.

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The 1-benzyl-3-[4-(methylamino)butyl]-2-benzimidazolinone used as the starting material was prepared in analogy to Example 18 from 1-[4-(methylamino)butyl]-2-benzimidazolinone via tert.-butyl methyl [4-(2-oxo-1-benzimidazoliny]butyl]carbamate.

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Example 25

W/C
P
In an analogous manner to that described in Example 17, by reacting [1S,2S]-2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl)ethyl p-toluenesulphonate and 1-[4-(methylamino)butyl]-3-(2-pyridylmethyl)-2-benzimidazolinone there was obtained 1-[4-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]methylamino]butyl]-3-(2-pyridylmethyl)-2-benzimidazolinone as an oil.

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The 1-[4-(methylamino)butyl]-3-(2-pyridylmethyl)-2-benzimidazolinone used as the starting material was prepared in analogy to Example 18 from tert.-butyl methyl [4-(2-oxo-1-benzimidazoliny]butyl]carbamate.

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Example 26

W/C
P
In an analogous manner to that described in Example 15, by reacting [1S,2S]-2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl)ethyl p-toluenesulphonate

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✓
5 and 1,3-dihydro-3-[6-(methylamino)hexyl]-2H -imidazo-
[4,5-c]pyridin-2-one there was obtained 3-[6-[[2-[[1S,2S]-
-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1 -isopropyl-2-
-naphthyl]ethyl]methylamino]hexyl]-1,3 -dihydro-2H-imidazo
dazo[4,5-c]pyridin-2-one as an oil.

✓
The 1,3-dihydro-3-[6-(methylamino)hexyl]-2H-imidazo-
[4,5-c]pyridin-2-one used as the starting material was
prepared as follows:

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In an analogous manner to that described in Example
17, from 6-(methylamino)-1-hexanol there was obtained
tert.-butyl methyl (6-hydroxyhexyl)carbamate as an oil
which was then converted via tert.-butyl methyl [6-
15 -[(methylsulphonyl)oxy]hexyl]carbamate, likewise obtained
as an oil, into tert.-butyl methyl [6-[1-(1-methylvinyl)-
-1,2-dihydro-2-oxo-3H-imidazo[4,5-c]pyridin-3-yl]hexyl]-
carbamate; the product was again obtained as an oil.

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12.2 g (31.4 mmol) of the last-named compound are
dissolved in 100 ml of ethanol, treated with 13 ml of
concentrated aqueous hydrochloric acid and heated to
reflux for 40 hours. Thereafter, the mixture is adjusted
to pH 9-10 with dilute aqueous sodium hydroxide solution
25 while cooling with ice, the reaction solution is saturated
with sodium chloride and extracted continuously with
chloroform for 16 hours. The extract is dried over
potassium carbonate and evaporated, whereby there are
obtained 7.2 g (92%) of 1,3-dihydro-3-[6-(methylamino)-
30 hexyl]-2H-imidazo[4,5-c]pyridin-2-one as an oil which is
processed without further purification.

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p
Example 27

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The following compounds were prepared in an analogous
manner to that described in Example 16:

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Example 29

The following compounds were manufactured in analogy to Example 28:

- 5
- [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-
-[[4-[p-(imidazol-1-yl)phenyl]butyl]methylamino]-
ethyl]-2-naphthyl methoxyacetate oxalate (1:1),
[α]_D²⁰ = +27.6° (c = 1%; methanol);
- 10
- [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-
-[methyl-[4-(3-isopropyl-2-oxo-1-benzimidazoliny)]-
butyl]amino]ethyl]-2-naphthyl methoxyacetate hydro-
chloride, [α]_D²⁰ = +27.6° (c = 1%; methanol);
- 15
- [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-
-[methyl-[6-(3-butyl-2-oxo-1-benzimidazoliny)]hexyl]-
amino]ethyl]-2-naphthyl methoxyacetate hydrochloride,
[α]_D²⁰ = +26.4° (c = 1%; methanol);
- 20
- [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-
-[methyl-[6-[3-(2-morpholinoethyl)-2-oxo-1-benz-
imidazoliny]]hexyl]amino]ethyl]-2-naphthyl methoxy-
acetate dihydrochloride, [α]_D²⁰ = +22.4° (c =
1%; methanol);
- 25
- [1S,2S]-2-[2-[[4-(3-benzyl-2-oxo-1-benzimidazoliny)]-
butyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-
1-isopropyl-2-naphthyl methoxyacetate hydrochloride,
[α]_D²⁰ = +25.6° (c = 1%; methanol);
- 30
- [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-
-[methyl-[4-[2-oxo-3-(2-pyridylmethyl)-1-benz-
imidazoliny]]butyl]amino]ethyl]-2-naphthyl methoxy-
acetate dihydrochloride, [α]_D²⁰ = +23.3° (c =
1%; methanol).
- 35

Example 30

1.3 g (3.1 mmol) of [1S,2S]-2-[2-[[3-(2-benz-
imidazolyl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-
5 -tetrahydro-1-isopropyl-2-naphthalenol in 10 ml of di-
methylformamide are treated at room temperature with
0.19 g (1.53 mmol) of 4-dimethylaminopyridine, 1.7 ml
(12.3 mmol) of triethylamine and a solution of 0.96 ml
(9.24 mmol) of isobutyryl chloride in 5 ml of dimethyl-
10 formamide and stirred at room temperature for 2 hours.
Thereafter, the reaction mixture is poured into 20 ml of
ice-water, treated with 10 ml of 1N aqueous sodium
hydroxide solution, stirred at 0° for 10 minutes and
extracted with 100 ml of methylene chloride. The extract
15 is washed with water, dried over potassium carbonate and
evaporated. The thus-obtained product is dissolved in
20 ml of methanol, treated with 1.5 ml of 1N aqueous
sodium hydroxide solution, stirred at room temperature for
1 hour, poured into 50 ml of water and extracted with
20 100 ml of methylene chloride. The extract is washed with
water, dried over magnesium sulphate and evaporated. The
residue is chromatographed on 30 g of silica gel with
methylene chloride and 1-20% isopropanol and on 20 g of
silica gel with methylene chloride/isopropanol/25% aqueous
25 ammonia (9:1:0.1). There are thus obtained 360 mg (21%) of
[1S,2S]-2-[2-[[3-(2-benzimidazolyl)propyl]methylamino]-
ethyl]-6-fluoro-1,2,3,4 -tetrahydro-1-isopropyl-2-naphthyl
isobutyrate dihydrochloride.

Example 31

A solution of 2.32 g (0.005 mol) of [1S,2S]-6-fluoro-
-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[5-(1-methyl-
-2-benzimidazolyl)pentyl]amino]ethyl]-2-naphthalenol and
35 0.6 g (0.005 mol) of phenyl isocyanate in 5 ml of toluene
is treated with 7.5 mg of tin(II) 2-ethylhexanoate and
heated to 100° for 15 hours. After concentration under

reduced pressure the oily residue is chromatographed on 160 g of silica gel with methanol/methylene chloride (3:2) as the elution agent. The oily product obtained is dissolved in methylene chloride and treated with an excess of hydrogen chloride in ether. There are obtained 2.15 g (65%) of [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[5-(1-methyl-2-benzimidazolyl)pentyl]-amino]ethyl]-2-naphthyl carbanilate dihydrochloride, m.p. 157-160°, as a colourless crystalline powder.

Example 32

The following compounds were obtained in an analogous manner to that described in Example 31:

- [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[5-(1-methyl-2-benzimidazolyl)pentyl]amino]ethyl]-2-naphthyl butylcarbamate dihydrochloride, m.p. 156-158°;

- [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[5-(1-methyl-2-benzimidazolyl)pentyl]amino]ethyl]-2-naphthyl benzylcarbamate dihydrochloride, m.p. 132-136°;

- [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl[5-(1-methyl-2-benzimidazolyl)pentyl]amino]ethyl]-2-naphthyl p-chlorocarbanilate dihydrochloride, m.p. 159-163°.

Example 33

A mixture of 4.67 g (11.5 mmol) of [1S,2S]-2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl)ethyl p-toluenesulphonate, 3.5 g (11.5 mmol) of 1-methyl-2-[3-(methylamino)propyl]-4,5-diphenylimidazole and 1.5 g (11.5 mmol) of N-ethyldiisopropylamine is

stirred at 100° for 1 hour. The cooled mass is partitioned between water and methylene chloride and the organic phase is washed with a saturated solution of sodium chloride, dried over sodium sulphate and concentrated to dryness.

5 The residual oil is chromatographed on 400 g of silica gel with methylene chloride/methanol (4:1) as the elution agent. The purified condensation product (5.3 of oil) is dissolved in 15 ml of methoxyacetic anhydride, treated with 0.85 ml of pyridine and the solution is stirred at
10 70° for 2 hours. The cooled reaction mixture is partitioned between 400 ml of methylene chloride and 400 ml of 3N aqueous sodium hydroxide solution and the mixture is stirred intensively at room temperature for 15 minutes. The separated aqueous phase is again extracted with 400 ml
15 of methylene chloride, the combined extracts are washed with a saturated aqueous solution of sodium chloride, dried over sodium sulphate and concentrated to dryness. The oily residue is chromatographed on 350 g of silica gel with methylene chloride/methanol (9:1) as the elution
20 agent. The oil obtained from the homogeneous fractions is dissolved in ethyl acetate and treated with an excess of hydrogen chloride in ether. The crystallizate is filtered off, washed with ether and dried. There are obtained 4.0 g (51%) of [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-
25 -2-[2-[[3-(1-methyl-4,5-diphenylimidazol-2-yl)propyl]-methylamino]ethyl]-2-naphthyl methoxyacetate dihydrochloride, m.p. 185-189°, as an almost colourless crystalline powder.

30 The 1-methyl-2-[3-(methylamino)propyl]-4,5-diphenylimidazole used as the starting material was prepared as follows:

P
31 3.2 ml (0.024 mol) of isobutyl chloroformate are added
35 dropwise at -5° to a solution of 7.0 g (0.024 mol) of 4,5-diphenylimidazole-2-propionic acid and 3.36 ml (0.024 mol) of triethylamine in 80 ml of dimethylformamide. After

4 stirring at 0-5° for 30 minutes 1.64 g (0.024 mol) of
methylamine hydrochloride and 3.36 ml (0.024 mol) of tri-
ethylamine in 32 ml of dimethylformamide and 1.65 ml of
5 water are added. The temperature is then left to rise to
room temperature and the mixture is stirred for a further
20 hours. After concentration under reduced pressure the
residue is boiled up in 250 ml of methanol and treated
with 3.6 ml (0.024 mol) of 1,8-diazabicyclo[5.4.0]undec-7-
-ene (DBU), whereby a clear solution results. 4.8 g of
10 N-methyl-4,5-diphenylimidazole-2-propionamide, m.p.
195-200° (dec.), result by cooling in an ice-bath. From
the mother liquor there are obtained by concentration and
treatment with water a further 2 g of the same product,
m.p. 195-200°. Total yield: 6.8 g (93%).

15 9.15 g (0.03 mol) of N-methyl-4,5-diphenylimidazole-2-
-propionamide are added portionwise to a stirred
suspension of 2.3 g (0.06 mol) of lithium aluminium
hydride in 160 ml of tetrahydrofuran and the mixture is
20 subsequently heated to reflux for 4 hours. At 5-10° there
are added dropwise thereto 6 ml of water, then 9 ml of a
10% solution of potassium hydroxide and again 6 ml of
water. The precipitate is filtered off and boiled up three
times with 50 ml of tetrahydrofuran each time. The
25 combined filtrates are washed with a saturated aqueous
solution of sodium chloride, dried over sodium sulphate
and concentrated to dryness under reduced pressure. The
oily residue is chromatographed on 200 g of silica gel
firstly with chloroform/ethanol (9:1) and then with
30 methanol as the elution agent. The first fractions which
are eluted homogeneous give, after evaporation and
trituration with ether, 1.2 g of starting material. The
following fractions which are eluted homogeneous yield,
after the same treatment, 5.5 g (73%) of 2-[3-(methyl-
35 amino)propyl]-4,5-diphenylimidazole in the form of
colourless crystals, m.p. 110-113°.

A solution of 5.25 g (0.018 mol) of 2-[3-(methyl-amino)propyl]-4,5-diphenylimidazole and 3.8 ml (0.028 mol) of benzyl chloroformate in 38 ml of dimethylformamide is treated with 5 g of finely ground dry potassium carbonate and thereupon stirred intensively at room temperature for 1 hour. The inorganic salts are then filtered off, washed with methylene chloride and the filtrate is concentrated to dryness under reduced pressure. The oily residue is chromatographed on 500 g of silica gel with ethyl acetate as the elution agent. The homogeneous fractions give, after evaporation and trituration of the residue with hexane, 6.5 g (85%) of 2-[3-(N-benzyloxy-carbonylmethylamino)propyl]-4,5-diphenylimidazole in the form of colourless crystals, m.p. 105-108°.

A solution of 6.4 g (0.015 mol) of 2-[3-(N-benzyloxy-carbonylmethylamino)propyl]-4,5-diphenylimidazole in 120 ml of dimethylformamide is treated at 15-20° under argon with 0.018 mol of sodium hydride (0.8 g of a 55% dispersion in mineral oil) and thereupon stirred at room temperature for a further 30 minutes. A solution of 1.85 ml (0.03 mol) of methyl iodide in 10 ml of dimethylformamide is added thereto at 15-20° within 15 minutes and the mixture is stirred at room temperature for a further 3 hours. After concentration under reduced pressure the residue is partitioned between ice-water and ethyl acetate. The organic phase, dried over sodium sulphate, is evaporated and the residual oil is chromatographed on 100 g of silica gel with ethyl acetate as the elution agent. The 2-[3-(N-benzyloxycarbonylmethylamino)propyl]-1-methyl-4,5-diphenylimidazole (6.4 g of oil) obtained is dissolved in 300 ml of methanol and hydrogenated at room temperature and normal pressure in the presence of 1 g of 5% palladium-on-active charcoal. The product, isolated in the usual manner, is chromatographed on 70 g of silica gel with methanol/concentrated ammonium hydroxide (100:1) as the elution agent. There are obtained 2.95 g (64%) of

✓
1-methyl-2-[3-(methylamino)propyl]-4,5-diphenylimidazole
as a thick oil.

Example 34

✓
5 In an analogous manner to that described in Example
33, [1S,2S]-2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-
-isopropyl-2-naphthyl)ethyl p-toluenesulphonate is reacted
firstly with 2-[3-(methylamino)propyl]-4,5-diphenylimi-
10 dazole and then with methoxyacetic anhydride. There is
obtained [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-
-2-[2-[[3-(4,5-diphenylimidazol-2-yl)propyl]methyl-
amino]ethyl]-2-naphthyl methoxyacetate dihydrochloride,
m.p. 160-164°, as a colourless crystalline powder.

14
15
Example 35

✓
14
P In an analogous manner to that described in Example
33, [1S,2S]-2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-
20 -isopropyl-2-naphthyl)ethyl p-toluenesulphonate is reacted
firstly with 2-[4-[(methylamino)methyl]benzyl]-1-methyl-
-benzimidazole and then with methoxyacetic anhydride.
There is obtained [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-
-isopropyl-2-[2-[[4-[(1-methyl-2-benzimidazolyl)methyl]-
25 benzyl]methylamino]ethyl]-2-naphthyl methoxyacetate
dihydrochloride, m.p. 130-134°, as an almost colourless
crystalline powder.

14
P The 2-[4-[(methylamino)methyl]benzyl]-1-methylbenz-
30 imidazole used as the starting material was prepared as
follows:

✓
P A mixture of 30 g (0.277 mol) of o-phenylenediamine
and 150 g of polyphosphoric acid ester (PPE) is heated to
35 120°. When the diamine has dissolved, 33 g (0.205 mol) of
p-cyanophenylacetic acid are added thereto in one portion
and the mixture is heated to 120° for a further 20

63

✓
minutes. After cooling to room temperature the viscous mass is treated with about 1 l of water and made weakly basic with solid sodium hydrogen carbonate. The mixture is extracted with methylene chloride and the extract is washed with water, dried over sodium sulphate and evaporated to dryness. Recrystallization of the residue from methylene chloride/ethyl acetate gives 29 g (60%) of 2-(p-cyanobenzyl)benzimidazole, m.p. 201-203°, as a colourless crystalline powder.

14
10 A solution of 21.9 g of 2-(p-cyanobenzyl)benzimidazole in a mixture of 140 ml of methanol and 140 ml of liquid ammonia is hydrogenated at room temperature and 30 bar in the presence of 5 g of Raney-nickel. The product, isolated in the usual manner, is chromatographed on 400 g of silica gel with methanol as the elution agent. The homogeneous fractions give, after evaporation and trituration of the residue with ether, 14.7 g (66%) of 2-[p-(aminomethyl)-benzyl]benzimidazole, m.p. 133-136°, as a pale brown crystalline powder.

14
20 A solution of 9.2 g (0.04 mol) of 2-[p-(aminomethyl)-benzyl]benzimidazole and 8.4 ml (0.06 mol) of benzyl chloroformate in 80 ml of dimethylformamide is treated with 10 g of finely ground dry potassium carbonate and thereupon stirred intensively at room temperature for 30 minutes. 12 ml (0.08 mol) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) are then added thereto and the mixture is stirred at room temperature for a further 30 minutes. The inorganic salts are filtered off, rinsed with methylene chloride and the filtrate is concentrated to dryness under reduced pressure. The oily residue is chromatographed on 600 g of silica gel firstly with methylene chloride/ethyl acetate (4:1) and then with chloroform/ethanol (9:1) as the elution agent. The fractions eluted with chloroform/ethanol give, after evaporation and trituration with ethyl acetate, 10.8 g (73%) of benzyl [4-[2-(benzimidazolyl)-

✓

64

14 methyl]benzyl]carbamate, m.p. 190-194°, as a colourless crystalline powder.

14 A solution of 8.9 g (0.024 mol) of benzyl [4-[2-(benz-
5 imidazolyl)methyl]benzyl]carbamate in 210 ml of dimethyl-
formamide is treated at 15-20° under argon with 0.056 mol
of sodium hydride (2.5 g of a 55% dispersion in mineral
oil) and thereupon stirred at room temperature for a
further 30 minutes. A solution of 7.4 ml (0.12 mol) of
10 methyl iodide in 22 ml of dimethylformamide is added
thereto at 15-20° within 20 minutes and the mixture is
stirred at room temperature for a further 10 minutes.
After concentration under reduced pressure the residue is
partitioned between ice-water and ethyl acetate. The
✓ 15 organic phase, dried over sodium sulphate, is evaporated
and the residual oil is chromatographed on 300 g of silica
gel with methylene chloride/ethyl acetate (1:1) as the
elution agent. The first fractions which are eluted homo-
geneous yield, after evaporation and trituration with
20 ether, 4.5 g (45%) of benzyl [4-[1-(1-methyl-2-benz-
imidazolyl)ethyl]benzyl]methylcarbamate, m.p. 131-133°, as
a colourless crystalline powder. The following fractions
which are eluted homogeneous give, after concentration,
3.5 g (37%) of benzyl [4-[(1-methyl-2-benzimidazolyl)-
25 methyl]benzyl]methylcarbamate as a viscous oil.

3.5 g of benzyl [4-[(1-methyl-2-benzimidazolyl)-
methyl]benzyl]methylcarbamate are dissolved in 600 ml of
methanol and hydrogenated at room temperature and normal
30 pressure after the addition of 1 g of 5% palladium-on-
-active charcoal. The product, isolated in the usual
manner, is chromatographed on 150 g of silica gel with
methanol/concentrated ammonium hydroxide (100:1) as the
elution agent. There are obtained 2.1 g (90%) of
35 2-[4-[(methylamino)methyl]benzyl]-1-methylbenzimidazole as
a thick oil.

65

Example 36

W/K
P
In an analogous manner to that described in Example
33, [1S,2S]-2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-
5 -isopropyl-2-naphthyl)ethyl p-toluenesulphonate is reacted
firstly with 2-[1-[4-[(methylamino)methyl]phenyl]ethyl]-
-1-methyl-benzimidazole and then with methoxyacetic
anhydride. There is obtained [1S,2S]-6-fluoro-1,2,3,4-
-tetrahydro-1-isopropyl-2-[2-[[4-[1-(1-methyl-2-benz-
10 imidazolyl)ethyl]benzyl]methylamino]ethyl]-2-naphthyl
methoxyacetate dihydrochloride (mixture of 2 epimers),
m.p. 95-105°, as an almost colourless crystalline powder.
A

The 2-[1-[4-[(methylamino)methyl]phenyl]ethyl]-1-
15 -methylbenzimidazole used as the starting material was
prepared in an analogous manner to that given in Example
35 by hydrogenating benzyl [4-[1-(1-methyl-2-benzimi-
dazolyl)ethyl]benzyl]methylcarbamate.

W/K
P
20 Example 37

In an analogous manner to that described in Example
33, [1S,2S]-2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-
-isopropyl-2-naphthyl)ethyl p-toluenesulphonate is reacted
25 firstly with 2-[4-[(methylamino)methyl]benzyl]benzimi-
dazole and then with methoxyacetic anhydride. There is
obtained [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-
-2-[2-[[4-[(2-benzimidazolyl)methyl]benzyl]methylamino]-
ethyl]-2-naphthyl methoxyacetate dihydrochloride, m.p.
30 146-150°, as an almost colourless crystalline powder.
A

The 2-[4-[(methylamino)methyl]benzyl]benzimidazole
used as the starting material was prepared as follows:

P
35 6.6 g (0.028 mol) of 2-(p-cyanobenzyl)benzimidazole
are heated to reflux for 2 hours in 110 ml of 1N sodium
hydroxide solution. The solution obtained is cooled and
66

14
5 extracted twice with 100 ml of ethyl acetate and twice with 100 ml of methylene chloride. The aqueous phase is adjusted to pH 6.0 with 2N hydrochloric acid and left to stand in an ice-bath for 30 minutes. The precipitate is filtered off under suction and washed with ether. There are obtained 5.8 g (83%) of p-[(2-benzimidazolyl)methyl]-benzoic acid, m.p. 265-267°, as a colourless powder.

31
10 2.8 ml of butyl chloroformate are added dropwise at -5° to a solution of 5.0 g (0.020 mol) of p-[(2-benzimidazolyl)methyl]benzoic acid and 2.8 ml (0.020 mol) of triethylamine in 68 ml of dimethylformamide. After
14 stirring at 0-5° for 30 minutes 1.32 g (0.020 mol) of methylamine hydrochloride and 2.8 ml (0.020 mol) of tri-
15 ethylamine in 28 ml of dimethylformamide and 1.4 ml of water are added. The temperature is then left to rise to room temperature and the mixture is stirred for a further 18 hours. After concentration under reduced pressure the residue is chromatographed on 400 g of silica gel with
20 chloroform/ethanol (4:1) as the elution agent. The uniform fractions give 2.0 g (38%) of N-methyl-p-[(2-benzimidazolyl)methyl]benzamide, m.p. 250-255° (dec.), as a colourless powder.

14
25 1.98 g (0.0075 mol) of N-methyl-p-[(2-benzimidazolyl)methyl]benzamide are added portionwise to a stirred suspension of 0.58 g (0.0075 mol) of lithium aluminium hydride in 40 ml of tetrahydrofuran and subsequently heated to reflux for 4 hours. At 5-10° there are added
30 dropwise 1.5 ml of water, then 2.3 ml of a 10% solution of potassium hydroxide and again 1.5 ml of water. The precipitate is filtered off and boiled three times with 20 ml of tetrahydrofuran each time. The combined filtrates are washed with a saturated aqueous solution of sodium
35 chloride, dried over sodium sulphate and concentrated to dryness under reduced pressure. The residue is chromatographed on 150 g of silica gel with methanol/concentrated

67

14 ammonium hydroxide (100:1) as the elution agent. There are
obtained 1.58 g (84%) of 2-[4-[(methylamino)methyl]-
benzyl]benzimidazole, m.p. 157-160°, as a colourless
crystalline powder.

5

Example 38

P ✓
10 In an analogous manner to that described in Example
33, [1S,2S]-2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-
-isopropyl-2-naphthyl)ethyl p-toluenesulphonate is reacted
firstly with 2-[trans-4-[(methylamino)methyl]cyclohexyl]-
benzimidazole and then with methoxyacetic anhydride. There
is obtained [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-iso-
propyl-2-[2-[methyl-[trans-4-(2-benzimidazolyl)cyclohexyl]-
15 methylamino]ethyl]-2-naphthyl methoxyacetate dihydro-
chloride, m.p. 150-153°, as a colourless crystalline
powder.

20 The 2-[trans-4-[(methylamino)methyl]cyclohexyl]benz-
imidazole used as the starting material was prepared as
follows:

P ✓
25 A solution of 20.3 g (0.07 mol) of trans-4-(N-benzyl-
oxycarbonyl-aminomethyl)cyclohexanecarboxylic acid in
380 ml of dimethylformamide is treated at 15-20° under
argon with 0.21 mol of sodium hydride (9.35 g of a 55%
dispersion in mineral oil) and thereupon stirred at room
temperature for a further 30 minutes. A solution of
17.5 ml (0.28 mol) of methyl iodide in 20 ml of dimethyl-
30 formamide is added thereto at 25-30° within 20 minutes and
the mixture is stirred at 70° for a further 1 hour. After
concentration under reduced pressure the residue is
partitioned between water and methylene chloride. The
organic phase is evaporated and the residual oil is
35 dissolved in a mixture of 350 ml of ethanol and 350 ml of
1N sodium hydroxide solution. The mixture is heated to
reflux for 1 hour, cooled and poured into 700 ml of ice-

✓
-water. The solution is extracted with ethyl acetate and then acidified with 6N hydrochloric acid. The liberated acid is extracted with methylene chloride and the extract is dried over sodium sulphate and evaporated. The residual
5 oil is chromatographed on 270 g of silica gel with a mixture of methylene chloride/ethyl acetate (4:1) as the elution agent. There are obtained 13.6 g (64%) of trans-4-(N-benzyloxycarbonyl-N-methyl-aminomethyl)cyclohexane-carboxylic acid as a thick oil.

10

31
31
A solution of 13.6 g (0.044 mol) of trans-4-(N-benzyloxycarbonyl-N-methyl-aminomethyl)cyclohexane-carboxylic acid and 9.5 ml (0.068 mol) of triethylamine in 110 ml of tetrahydrofuran is treated at -15° within 30
15 minutes with 6.5 ml (0.049 mol) of isobutyl chloroformate. A solution of 5.8 g (0.053 mol) of o-phenylenediamine is then added dropwise at -15° within 45 minutes. The mixture is stirred at room temperature for 1 hour and left to stand for 20 hours. After concentration under reduced
20 pressure the residue is partitioned between water and ethyl acetate and the organic phase is washed with a 5% solution of sodium hydrogen carbonate, then with a saturated aqueous solution of sodium chloride and finally with water. The solution, dried over magnesium sulphate,
25 is evaporated and triturated with ether. The solid product obtained (9.3 g) is dissolved in 200 ml of toluene, 3 g of p-toluenesulphonic acid are added thereto and the mixture is heated to reflux for 4 hours with a water separator. The solution is cooled, washed with a 2N sodium carbonate
30 solution and a saturated aqueous solution of sodium chloride, dried over magnesium sulphate and concentrated to dryness under reduced pressure. The solid residue is recrystallized from ethyl acetate. There are obtained
35 5.6 g of benzyl [[trans-4-(2-benzimidazolyl)cyclohexyl]-methyl]methylcarbamate, m.p. 146-148°, as a colourless crystalline powder. After chromatography on 250 g of
14 silica gel with ethyl acetate/methylene chloride (9:1) as

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the elution agent the mother liquor gives a further 1.1 g of the same product, m.p. 146-148°. Total yield: 6.7 g (40%).

5 6.0 g of benzyl [[trans-4-(2-benzimidazolyl)cyclohexyl]methyl]methylcarbamate are dissolved in 600 ml of ethanol and hydrogenated at room temperature and normal pressure after the addition of 1 g of 5% palladium-on-active charcoal. The product, isolated in the usual
10 manner, is recrystallized from methylene chloride/ether. There are obtained 3.0 g (78%) of 2-[trans-4-[(methylamino)methyl]cyclohexyl]benzimidazole, m.p. 232-235°, as a colourless crystalline powder.

15 Example 39

In an analogous manner to that described in Example 33, [1S,2S]-2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl)ethyl p-toluenesulphonate is reacted
20 firstly with 2-[trans-4-[(methylamino)methyl]cyclohexyl]-1-methyl-benzimidazole and then with methoxyacetic anhydride. There is obtained [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-[methyl-[trans-4-(1-methyl-2-benzimidazolyl)cyclohexyl]methylamino]ethyl]-2-naphthyl
25 methoxyacetate dihydrochloride, m.p. 148-152°, as a colourless crystalline powder.

The 2-[trans-4-[(methylamino)methyl]cyclohexyl]-1-methyl-benzimidazole used as the starting material was
30 prepared as follows:

A solution of 7.2 g (0.019 mol) of benzyl [[trans-4-(2-benzimidazolyl)cyclohexyl]methyl]methylcarbamate in 160 ml of dimethylformamide is treated at 15-20° under
35 argon with 0.023 mol of sodium hydride (1.0 g of a 55% dispersion in mineral oil) and thereupon stirred at room temperature for a further 30 minutes. A solution of 2.3 ml

(0.038 mol) of methyl iodide in 10 ml of dimethylformamide is added thereto at 15-20° within 15 minutes and the mixture is stirred at room temperature for a further 3 hours. After concentration under reduced pressure the residue is partitioned between ice-water and ethyl acetate. The organic phase, dried over sodium sulphate, is evaporated and the solid residue is recrystallized from ethyl acetate/ether. There are obtained 5.9 g (79%) of benzyl [[trans-4-(1-methyl-2-benzimidazolyl)cyclohexyl]-methyl]methylcarbamate, m.p. 141-142°, as a colourless crystalline powder.

5.9 g of benzyl [[trans-4-(1-methyl-2-benzimidazolyl)-cyclohexyl]methyl]methylcarbamate are dissolved in 600 ml of ethanol and hydrogenated at room temperature and normal pressure after the addition of 1 g of 5% palladium-on-active charcoal. The product, isolated in the usual manner, is chromatographed on 250 g of silica gel firstly with methylene chloride/methanol (1:1) and then with methanol/concentrated ammonium hydroxide (100:1) as the elution agent. There are obtained 3.3 g (85%) of 2-[trans-4-[(methylamino)methyl]cyclohexyl]-1-methyl-benzimidazole as a thick oil.

Example 40

In an analogous manner to that described in Example 7, by reacting 2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1 α -isopropyl-2 β -naphthyl)ethyl p-toluenesulphonate and 3,4-dihydro-4-methyl-1-[4-(methylamino)butyl]-2H-1,4-benzodiazepine-2,5-(1H)-dione there is obtained 1-[4-[[2-[[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]methylamino]butyl]-3,4-dihydro-4-methyl-2H-1,4-benzodiazepine-2,5-(1H)-dione, MS: M⁺ 509.

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✓
In an analogous manner to that described above, starting from 2-(6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1 α -isopropyl-2 β -naphthyl)ethyl p-toluenesulphonate and (S)-6-chloro-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]-benzodiazepine-5,11-(10H)-dione there was prepared
5 (S)-6-chloro-10-[4-[[2-[[1S,2S]-6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1-isopropyl-2-naphthyl]ethyl]methylamino]-butyl]-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11-(10H)-dione, MS: M⁺ 570.

10

The 3,4-dihydro-4-methyl-1-[4-(methylamino)butyl]-2H-1,4-benzodiazepine-2,5-(1H)-dione used as the starting material was prepared as follows:

P
15 10 g (40 mmol) of 4-[1-(benzyloxy)-N-methylformamido]-butyric acid are dissolved in 200 ml of ethanol and treated with 1 ml of concentrated sulphuric acid. Thereafter, the reaction mixture is heated to reflux for 4 hours and the solvent is subsequently evaporated off. The
20 reaction product is then extracted with methylene chloride/saturated sodium bicarbonate solution. After drying and evaporation of the extract there are obtained 9.24 g of a brown oil which is dissolved in 200 ml of tetrahydrofuran, treated with 7.1 ml of 10M boron
25 methylsulphide complex and heated to reflux for 2 hours. Thereafter, the reaction mixture is left to stand at room temperature overnight and then sufficient methanol is slowly added thereto so that gas evolution no longer occurs. In this manner there is obtained a clear solution
30 which is evaporated. The residue obtained (8.09 g) is chromatographed on silica gel with a 1:1 mixture of ethyl acetate and hexane, whereby there are obtained 6.82 g (72%) of benzyl (4-hydroxybutyl)methylcarbamate which is used directly in the next step.

35

6.75 g (28.4 mmol) of the carbamate obtained above and 10.0 g (52.5 mmol) of p-toluenesulphonyl chloride are

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dissolved in 25 ml of pyridine at 0°. After standing for 6 hours the mixture is added to ice and extracted with ether. The ether extract is washed with 4N hydrochloric acid, saturated sodium bicarbonate solution and saturated sodium chloride solution, dried and evaporated. In this manner there are obtained 9.38 g (84%) of a yellowish oil of benzyl methyl [4-[(p-toluenesulphonyl)oxy]butyl]-carbamate which is processed directly.

1.9 g (10 mmol) of 4-methyl-3H-1,4-benzodiazepine-2,5-(1H,4H)-dione are dissolved in 20 ml of dimethylformamide and added to a suspension of 430 mg (10 mmol) of 55% sodium hydride in 50 ml of dimethylformamide. 30 minutes after the addition a solution of 3.91 g (10 mmol) of benzyl methyl [4-[(p-toluenesulphonyl)oxy]butyl]-carbamate in 20 ml of dimethylformamide is added and the whole reaction mixture is stirred at room temperature for 20 hours. Thereafter, the solvent is evaporated under reduced pressure at 50° and water is subsequently added. After two-fold extraction with methylene chloride the solvent is again evaporated and the residue is chromatographed on silica gel with a 20:1 mixture of methylene chloride and methanol, whereby there are obtained 3.92 g (95.8%) of benzyl methyl [4-(2,3,4,5-tetrahydro-4-methyl-2,5-dioxo-1H-1,4-benzodiazepin-1-yl)butyl]carbamate, MS: M^+ 409.

The above carbamate is converted in an analogous manner to that described in Example 7, last paragraph, into the desired 3,4-dihydro-4-methyl-1-[4-(methylamino)-butyl]-2H-1,4-benzodiazepine-2,5-(1H)-dione which is used directly in the next step.

In an analogous manner to that described above, starting from benzyl methyl-[4-[(p-toluenesulphonyl)oxy]butyl]carbamate by reaction with the corresponding benzodiazepine there was prepared (S)-6-chloro-

-1,2,3,11a-tetrahydro-10-[4-(methylamino)butyl]-5H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11-(1OH)-dione.

Example 41

5

The following compounds were prepared in an analogous manner to that described in Example 8 by methoxyacetylating the corresponding hydroxy derivatives:

10 - [1S,2S]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-[2-
-[[4-(2,3,4,5-tetrahydro-4-methyl-2,5-dioxo-1H-1,4-
-benzodiazepin-1-yl)butyl]methylamino]ethyl]-2-
-naphthyl methoxyacetate hydrochloride, $[\alpha]_{589}^{20}$
= +28.2° (c = 0.5%; methanol);

15

✓ 15 - [1S,2S]-2-[2-[[4-[(S)-6-chloro-2,3,11,11a-tetrahydro-
-5,11-dioxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-
-10(5H)-yl]butyl]methylamino]ethyl]-6-fluoro-1,2,3,4-
-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate
20 hydrochloride, $[\alpha]_{589}^{20}$ = +215.2° (c = 0.5%;
methanol).

25

30

35

Example A

Tablets

5 Composition:

10	1) 2-[2-[[3-(2-Benzimidazolyl)propyl]methyl- amino]ethyl]-6-fluoro-1,2,3,4-tetrahydro- -1 α -isopropyl-2 α -naphthyl methoxyacetate hydrochloride	75 mg
	2) Lactose powdered	135 mg
	3) Maize starch white	55 mg
	4) Povidone K 30 (polyvinylpyrrolidone)	15 mg
	5) Maize starch white	15 mg
15	6) Talc	3 mg
	7) Magnesium stearate	<u>2 mg</u>
	Tablet weight	300 mg

Manufacturing procedure:

20

1-3 are mixed intensively. The mixture is thereafter
moistened with an aqueous solution of 4 and kneaded, and
the resulting mass is granulated, dried and sieved. The
granulate is mixed with 5-7 and pressed to tablets of
suitable size.

25

30

35

Example B

Tablets

5 Composition

1)	2-[2-[[3-(2-Benzimidazolyl)- propyl]methylamino]ethyl]- -6-fluoro-1,2,3,4-tetrahydro- -1 α -isopropyl-2 α -naphthyl methoxyacetate hydrochloride	75 mg	60 mg
2)	Lactose powdered	100 mg	100 mg
3)	Maize starch	60 mg	60 mg
4)	Povidone K 30		
15	(polyvinylpyrrolidone)	5 mg	5 mg
5)	Maize starch	15 mg	15 mg
6)	Sodium carboxymethylstarch	5 mg	5 mg
7)	Talc	3 mg	3 mg
8)	Magnesium stearate	<u>2 mg</u>	<u>2 mg</u>
20	Tablet weight	265 mg	250 mg

✓ Manufacturing procedure:

1-3 are mixed intensively. The mixture is thereafter
moistened with an aqueous solution of 4 and kneaded, and
the resulting mass is granulated, dried and sieved. The
granulate is mixed with 5-8 and pressed to tablets of
suitable size.

Example C

Tablets

5 Composition:

1)	2-[2-[[3-(2-Benzimidazolyl)- propyl]methylamino]ethyl]- -6-fluoro-1,2,3,4-tetrahydro		
10	-1 α -isopropyl-2 α -naphthyl methoxyacetate hydrochloride	75 mg	90 mg
	2) Lactose powdered	46 mg	46 mg
	3) Cellulose microcrystalline	60 mg	60 mg
	4) Povidone K 30		
15	(polyvinylpyrrolidone)	10 mg	10 mg
	5) Sodium carboxymethylstarch	4 mg	4 mg
	6) Talc	3 mg	3 mg
	7) Magnesium stearate	<u>2 mg</u>	<u>2 mg</u>
	Table weight	200 mg	215 mg

20

Manufacturing procedure:

1-3 are mixed intensively. The mixture is thereafter
moistened with an aqueous solution of 4 and kneaded, and
25 the resulting mass is granulated, dried and sieved. The
granulate is mixed with 5-7 and pressed to tablets of
suitable size.

30

35

Example D

Capsules

5 Composition:

1)	2-[2-[[3-(2-Benzimidazolyl)propyl]methyl- amino]ethyl]-6-fluoro-1,2,3,4-tetrahydro- -1 α -isopropyl-2 α -naphthyl methoxyacetate hydrochloride	75 mg
2)	Lactose crystalline	100 mg
3)	Maize starch white	20 mg
4)	Talc	9 mg
5)	Magnesium stearate	<u>1 mg</u>
15	Capsule fill weight	205 mg

Manufacturing procedure:

20 The active substance is mixed intensively with the
lactose. This mixture is thereafter admixed with the maize
starch, the talc and the magnesium stearate, and the
mixture is filled into capsules of suitable size.

25

30

35

Example E

Capsules

5 Composition:

1)	2-[2-[[3-(2-Benzimidazolyl)propyl]methyl- amino]ethyl]-6-fluoro-1,2,3,4-tetrahydro- -1 α -isopropyl-2 α -naphthyl methoxyacetate	
10	hydrochloride	75 mg
2)	Cellulose microcrystalline	100 mg
3)	Sodium carboxymethylstarch	5 mg
4)	Talc	9 mg
5)	Magnesium stearate	<u>1 mg</u>
15	Capsule fill weight	190 mg

Manufacturing procedure:

20 The active substance is mixed intensively with the
cellulose. This mixture is thereafter admixed with the
sodium carboxymethylstarch, the talc and the magnesium
stearate, and the mixture is filled into capsules of
suitable size.

25 Example F

Injection solution

		<u>1 ml</u>
30	2-[2-[[3-(2-Benzimidazolyl)propyl]methyl- amino]ethyl]-6-fluoro-1,2,3,4-tetrahydro- -1 α -isopropyl-2 α -naphthyl methoxyacetate hydrochloride	8 mg
35	Sodium chloride crystalline pure	8.5 mg
	Water for injection	ad 1 ml

Example G

✓ When the procedures described in Examples A-F are followed, tablets, capsules and injection preparations can be manufactured from the following, likewise preferred, compounds and their pharmaceutically usable salts:

- 5
- 10
- [1S,2S]-2-[2-[[3-(2-benzyimidazolyl)propyl]methyl-amino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate hydrochloride,
- 15
- [1S,2S]-2-[2-[[5-(2-benzthiazolyl)pentyl]methyl-amino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate hydrochloride.

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